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Specification, as originally filed, with Application for Patent Serial No: **2,368,708**, on January 14, 2002, by **WILLIAM HERMAN**, for "Multifunctional Ligand".

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Multifunctional Ligands

Field of The Invention

The present invention relates multispecific ligand, for example a heterofunctional ligand comprising first and second binding moieties which have cooperating functional affinities as well as a multifunctional ligand, for example, a bi-specific antibody, having at least a first portion which binds to a 'lymphatic vessel associated' antigen/receptor and a second portion having at least one immune-affecting functionality including, without limitation, functions related to antigen presentation, immune signaling, suppression or enhancement of immune tolerance or immune stimulation, or binding to a target molecule, for example a cell surface antigen, receptor etc.

Background of the Invention

Immunotherapy has gained wide acceptance as a promising measure to address several disease states including autoimmune disease, transplant rejection, infectious disease and cancer. Despite rapid and exciting progress in approaches to treatment, the disease burden attributable to such illnesses has not significantly abated. The complex nature of the normal and pathologic immunologic processes associated with such diseases, coupled with logistical problems in evaluating and implementing methods for immunotherapy in human subjects, continue to be some of the obstacles to successful advances in treatment.

Successful approaches to immunotherapy are predicated on the ability of the immunotherapeutic molecule to be delivered in a therapeutic, sub-toxic dose at the desired therapeutic frequency. In the process of selection of a suitable therapeutic molecule, it is recognized that sub-toxic doses may be insufficient for the desired therapeutic effect, especially where the antibody binds incidentally to cell populations other than the target population. In the case of an injectable preparation and especially an intravenous mode of delivery, in contrast to readily self-administered modes of delivery, the optimal dosing frequency for therapeutic purposes could impose an undesirable burden on the patient and care-giver, assuming that such optimal frequency is to begin with deemed convenient for clinical trials.

Numerous research efforts are underway to identify and test ligands including antibodies, agonists, antagonists etc. which will bind to or otherwise interact with or trigger responses in or towards immune and other cells, for example pathogenic organisms and diseased cells. A recent example is a renewed interest to find molecules and methods of triggering an interaction with CD45 (see for example Nature (2001) Vol. 409 p. 349-354).

Summary of the Invention

The present invention facilitates development, therapeutic evaluation, and delivery, particularly targeted delivery of molecules that exert therapeutic functions and particularly immune functions. In preferred aspects the invention contemplates compositions of matter and methods of delivery, in some cases using ligands that but for the targeting methods herein defined would be ineffective or have a broader effect than is desirable; or similarly, but for the severity of the disease or the absence of other therapeutic alternatives for which such ligands are useful, they would otherwise be inappropriate for therapeutic use. The present invention accommodates evaluation of such ligands for therapeutic purposes using such targeting strategies.

According to one aspect, the invention is directed to a multispecific ligand[1] with at least two different binding specificities for different target ligands on the same target cell[2] and adapted to bind simultaneously to the different target ligands, said multispecific ligand comprising a first target binding moiety which preferentially[3] recognizes a first target ligand and a second target binding moiety which preferentially recognizes a second target ligand, and wherein the ability of the second target binding moiety to bind to the second target ligand is diminished relative the ability of the first target binding moiety to bind to the first target ligand, the first target binding moiety having an ability to bind to the first target ligand which is at least sufficient for the first target moiety to bind to the first target ligand independently of the second target binding moiety binding to the second target ligand and an off-rate which at least sufficiently exceeds the on-rate of the second target binding moiety for the second target ligand to provide at least provide opportunity for the second target moiety to bind the second target ligand when the first target binding moiety is bound to first target ligand, the second target binding moiety having a relatively diminished ability to bind and/or stay bound to the second target ligand independently of the binding of the first target binding moiety to the first target ligand (such that a plurality of the multispecific ligand will bind to a population of cells bearing both target ligands ***in preference[4] to*** a population of cells bearing only the second target ligand (ie. at least

[1] The term multi means at least two and the term ligand is used broadly to refer to any entity or part thereof which can be subject to an intermolecular interaction that can result in binding

[2] The term cell is used to mean any cell and any infectious agent, immune target or parasite (including, without limitation, spores, viruses, baceria, fungi)

[3] some cross-reactivity(s) does not preclude the utility of the invention

[4] This term needs to be understood in terms of baseline of expected augmented binding where there are two targets on the same cell even were the abilities to bind or stay bound to be comparable.

in part due to the first target binding moiety assisting the second target binding moiety to bind to the second target ligand and out of proportion to what could be statistically attributed to the presence of two targets ligands on the target cell ie. the binding of the first target binding moiety assisting the second target moiety to bind is relatively increased and the binding of the second target binding moiety assisting the first target binding moiety to bind to the first target ligand is preferably independently decreased).

In one embodiment, said first target binding moiety recognizes a target cell-associated* target ligand, for example a ligand which is exclusively expressed, primarily expressed or over-expressed to advantage on the target cell population and said second target binding moiety recognizes a non-target cell-associated target ligand which is present on target cells and non-target cells, for example a receptor, including a decoy receptor eg. for TRAIL. The multispecific ligand is thereby adapted to block or activate the receptor primarily on the target population of cells. In this connection, the invention is also directed to methods of evaluating or implementing the effects of this enhanced selectivity for the receptor on the target cell population and can be employed to diminish the adverse consequences and evaluate the benefits associated with using a ligand binding moiety that would otherwise undesirably bind to receptors on non-target cells.

The invention contemplates a variety of different strategies that can be used alone, or in any variety of compatible permutations to differentiate between target cells and/or between target and non-target cells. The choice of strategies, may depend at least in part on the circumstances, including the nature of the fluid environment in question, including the rapidity and pressure of flow and the direction(s) of this pressure, the method of delivery, the medical condition for which the molecule is being evaluated, whether the target is moving or stationary, or both, the location or various locations of the target, the targeting venue or venues that is/are most effective and the importance of the size of the molecule for reaching the target, and the importance of creating immunoconjugates and immunofusions with other molecules. The invention contemplates that employing more than one than one type of construct would be desirable and the invention is therefore directed to the various combinations and permutation of constructs according to the invention, in combination with each other and other therapeutic molecules or modalities. One of constructs contemplated by the invention, is a multispecific antibody, for example a bispecific antibody or fragment thereof having a configuration which allows for binding to two antigens on the same cell, for example a traditional four chain immunoglobulin configuration, a diabody configuration (depending on the relative positions of the target ligands) and others herein referenced and known to those skilled in the art. These strategies are set forth below:

Strategies

According to one embodiment, the intrinsic affinity of the first target binding moiety for the first target is greater than the intrinsic affinity of the second target binding moiety for the second target. The term "intrinsic" affinity is used to connote a measure of the affinity of a given target binding moiety for its target ligand which is independent of the affinity of the at least one other target binding moiety for its target ligand and as used herein could theoretically be evaluated, if the other target binding moiety had an irrelevant specificity and therefore could not bind to its target ligand, such evaluation taking into account the size and weight distribution of the molecule.

According to another embodiment, the relative on-rate* of the first target binding moiety is greater than the relative on-rate of the second target binding moiety. The term relative on rate is used to connote an effective difference in on-rate that may be instrinsic to the individual target binding ligand or may attributable to its configuration or relationship vis-à-vis other parts of the molecule.

Where the intrinsic on-rate[5] of the first target binding moiety is greater than the intrinsic on-rate of the second target binding moiety, the invention contemplates that the off-rate contribution to the affinity of the first target binding moiety may be proportionally greater than the off-rate contribution to the affinity of the second target binding moiety. The invention contemplates that the binding of the second target ligand binding moiety to its target ligand may be more effective if its lower affinity is attributable in part due its reduced on-rate. The invention contemplates methods for reducing the affinity a target binding moiety by reducing its on rate for example by mutating or adding amino acid residues in regions of the VH or VL that don't directly contribute to the off-rate (of a relatively high affinity binder for the target, for example, as determined by modeling and structural analysis, for example, by evaluating x-ray crystal structure and evaluating NMR data of the binding, or by mutagenesis, preferably by introducing a diversity of changes in a high-throughput manner (eg. phage display, ribsome display,microarray or other expression library) including substitutions, additions and deletions within various regions of the VH or VL and determining their effect. For example, the invention contemplates that the second target binding moiety is generated using a library characterized by members in which one of the regions of VH or VL, including particularly the CDR1 and CDR2, for example the CDR1 of the VH or CDR2 of the VL, is shortened and/or mutated in a manner to reduce the probability of its having any direct contribution to the affinity of the selected molecule (through molecular interaction), for example mutated to introduce amino acids that are least important for intermolecular interactions, for example by minimizing the occurrence of amino acids that are important for electrostatic interactions and optionally also hydrogen binding, generating a binder whose affinity will be postulated to be independent of the contribution of the modified CDR, and then optionally evaluating the success of this latter step through further mutagenesis (this step is most revealing if the CDR is shortened but not mutated or mutated to

[5] The actual on-rate if the on-rate was to be measured independently of the on-rate of the other binding moiety but otherwise taking into account

introduce amino acids important for intermolecular interactions) and then using the library to incrementally lengthen the region and/or introduce amino acids important for intermolecular interaction at a distance (eg. electrostatic interactions and optionally also hydrogen binding) to introduce minimal steric hindrance or intermolecular repulsion. The invention also contemplates that introducing amino acids that have the greatest potential for hydrogen bonding will introduce an aqueous cushion into the interface region with the target ligand to diminish the on-rate contribution to affinity. The invention also contemplates modifying the amino acid composition of an existing binder by introducing or one or amino acids or mutations into a framework region at a location which is proximal to the binding region or a region which borders the interface of approach to the binding region or any interface between the target binding moiety and the target ligand. The invention contemplates that the on-rate and off-rate can be routinely measured using various technologies (eg. Biacore) known to those skilled in the art, including techniques of measuring these rates in real-time (Biosite). In one embodiment of the method the antibodies have peptide tags that link them to their DNA eg a phage (as per techniques publsished in the art) and the antibodies are evaluated independently of the phage or other expression system linkage which allows a more accurate measure of their true on rates and off-rates. The invention also contemplates that FR1 could be lengthened in a relatively high affinity second target binding moiety to reduce its on rate. The invention also contemplates that an antibody having a reduced on rate could be fused to a toxin such as a truncated version of PE to better ensure its diffusion throughout a tumor since a single immunotoxin molecule is theoretically sufficient to kill the cell, and that a reduced on-rate will diminish the number of molecules binding to cells in the area of highest concentration of the immunotoxin. The invention contemplates that the reduced affinity is portioned between the on-rate and off-rate and a higher on-rate lower off-rate Ab could be delievered in alternating days or other cycles of treatment. Thus the invention is directed to an antibody conjugated or fused to a functional moiety, wherein the on-rate contribution to the affinity of the antibody is anywhere between 5x and two order of magnitudes less than typical molecules having suitable properties for diffusion including each of molecules having anywhere (any increments) between 10^{-7} and 10^{-10} molar affinities (eg. $5x\ 10^{-7}$, $3x10^{-8}$) preferably increments between 10^{-8} to 10^{-10} (on rate approx. 10^{-8}) molar affinities, more preferably increments between $5x10^{-8}$ and $5x10^{-9}$.

In another aspect the invention contemplates that the multispecific ligand may comprise an Fc portion and a hinge portion and that one or both of a) the length, amino acid composition or[6] molecular weight (or various combinations of these interrelated factors) of the Fab or Fc portion; and b) the amino acid composition[6] of hinge portion[7] are selected to reduce the circumstantial[8] affinity of the second ligand binding moiety where the first ligand binding moiety is unbound relative to the circumstantial affinity of the second ligand binding moiety where the first ligand binding moiety is bound. The term circumstantial affinity broadly contemplates that the length and molecular weight of the Fc and the flexibility of the hinge region will individually and collectively contribute to the affinity of the molecule in proportion the shear rate of the fluid environment to a degree depending on whether the target is stationary or moving, once the multispecific ligand is bound. If bound via the second target binding moiety, any increase in the molecular weight especially a distribution of the molecular weight towards the Fc or first ligand binding moiety will serve as a lever in a moving fluid environmrnt, to favor disengagement from binding especially since the off-rate of this binding arm is relatively low to begin with. This same lever effect will impinge on the binding on the binding of the first ligand binding moiety but to a lesser degree due to its higher affinity. Where the hinge region is extra flexible or has several regions of flexibility (for example where the heavy chains are linked through several disulfide bonds with regions of flexibile linker therebetween) the effect on the individual and paired binding of both the first and second target binding moieties will be less. On the other hand, decreasing the flexibility of the hinge region by alteration to its length and/or amino acid composition and increasing the molecular weight distribution towards the "free" end of the Fc will affect all binding scenarios to a greater extent. The latter strategy may be less desirable where the Fab of the first target binding moiety is lengthened to increase its propensity for individual binding. For example, in a conventional four chain or heavy chain antibody (two heavy chains but no light chains) the hinge region could be shortened on the amino terminus side of the disulfide bond linking the heavy chains to an extent that does interfere with the simultaneous binding to both the first and second target binding moieties. The invention also contemplates that the target cell environment, naturally or through intervention, is a fluid environment (low shear rate) or enzyme environment which will favor a greater impact on disengagement of the second ligand binding moiety, in the case of an enzyme, one which will cleave an Fc into which a cleavage site has been introduced so that disengagement due to the lever effect will primarily impinge on binding of the second ligand moiety to the non-target cell population (eg. low shear rate or presence of MMP type enzymes in a targeted solid tumor environment).

The invention also contemplates that the intrinsic[8] affinity of the second ligand binding moiety is greater when the first ligand binding moiety is bound to the first target ligand relative to when it is unbound. For example the invention contemplates that second ligand binding moiety is selected in an environment in which there is a selective pressure (moderate fluid flow eg. using live cells or tissue, candidate ligand binding molecules or pairs of the target ligands on latex beads, where the substrate to which they are bound is on an incline or otherwise subject to fluid

[6] includes length

[7] any polypetide segment that serves as means for linking two typically heavy chains, eg. through one or more disulfide bonds, leucine zipper fos-jun, optionally a flexible hinge typical of an IgG1 or having one to several more disulfide bonds eg. IgG3.

[8] shear rate, presence of degrading enzymes

flow, optionally with rigid or high mol. weight Fc) for simultaneous binding so that the affinity of the second ligand binding moiety is selected on the basis of its ability to augment the binding affinity of a first ligand binding moiety of preselected affinity for the first target ligand (after or optionally before its affinity maturation, depending on the shear force and affinity in question) and thereby augment the affinity of the multispecific binding ligand as a whole, while the first ligand binding moiety is bound. In this way, the strength of the binding affinity of the second ligand may be predicated on the first ligand moiety being bound. The foregoing strategy may have accentuated or at least equal application where the first ligand binding moiety has a longer Fab or for example where both the first and second ligand binding moiety are devoid of a light chain ie. where having the correct binding interface for the second target binding moiety might be more acute. The invention contemplates that the individual affinity of second ligand binding moiety selected in the above manner would be tested to ensure that its individual affinity was not sufficient for substantial independent targeting.

It will be appreciated that the foregoing strategies could be employed for designing a multispecific ligand which will primarily target cells which have both the first and second target ligand (eg. where the ligands together are present primarily on the target cell population) even where neither target ligand is individually found primarily on the target cell population, by employing a multispecific ligand in which neither target ligand is of sufficient affinity in the circumstances to effectively (with effect) bind or remain bound without the other target ligand being available for simultaneous binding. As suggested above, it will be appreciated that a relatively high affinity ligand could initially be employed on one of the ligand binding arms to select a moderate affinity ligand binding arm which is individually insufficient for targeting its target on non-target cells in the circumstances in which it will be employed, and that the high affinity ligand binding arm can subsequently be reduced to moderate affinity with similar lack of individual effect. In one embodiment, this construct can be employed to evaluate the effect of blocking two receptors on the same cell, for example chemokine receptors eg. CCR7 and CXCR4 on a breast cancer cell. In one embodiment, the off-rate of one or optionally both ligand binding moities is sufficient in the circumstances to permit the moiety to remain bound for a sufficient duration for the other moiety to bind ie. it exceeds its effective or intrinsic on-rate.

In connection with the foregoing and ensuing strategies it will also be appreciated that the hinge region may be lengthened on the N-terminal side of the most N-terminus linker between the heavy chains so as to permit greater flexibility in the binding of different antigens at different possible proximities to one another.

With respect to each of the preceding aspects of the invention, the invention also directed to a multispecific ligand comprising a first ligand moiety which recognizes a first target ligand that is over-expressed on a disease associated entity for example a diseased or disease-causing or mediating cell or infectious agent and a second ligand binding moiety that recognizes a target ligand which is characterized in that 1) it does not lend itself to facilitating or permitting internalization of the second ligand binding moiety; 2) it is expressed on non-diseased cells that are proximal to or border a disease-associated entity (eg. a diseased, disease causing or mediating cell or infectious agent). According to one embodiment, the affinity of the second ligand binding moiety for the second target ligand is reduced, for example due at least in part to having a lower on-rate, so that the multispecific ligand will more readily migrate through a non-diseased tissue bordering a diseased cell or tissue eg. a tumor. Further, the invention contemplates that the first ligand binding moiety has a reduced affinity, for example, at least in part due having a reduced on-rate. Thus the invention contemplates that a population of the previously described multispecific ligand will have a proclivity to bind to cells in the region of tumor cell invasion and simultaneously to both types of cells. In one embodiment the invention also contemplates that the first target binding moiety may have a) a higher off-rate and/or an on-rate/off-rate which increases the propensity of the multispecific ligand to bind to adjacent diseased non-diseased cells due to the adjacent presence of both target ligands (the above-mentioned strategies for generating a binder that binds preferentially when both target ligands are present can be adapted to a substrate such as immediately adjacent preferably cell sized latex beads each having a density of one of the target ligands or columnar packing materials or flat substrates having a high density dispersion of both target ligands. In connection with the foregoing, the invention contemplates that a variety of different effector platform may be employed with varying effect on the non-diseased cells. For example, a superantigen platform or immunocytokine approach should have a minimal effect on normal cells, the ADEPT type methodogies might well have some effect on normal cells, and radionuclide effect will have varied effects depending on the choice of radionuclide; in each case the effects will be exerted to a degree depending on the affinity of the multispecific ligand for non-diseased cells. According to one embodiment, the invention contemplates that the first target binding moiety binds to a target ligand that permits or facilitates internalization of the multispecific ligand. In this connection the invention contemplates that the first target binding moiety may have a higher affinity and will be fused or conjugated to a polypeptide comprising a functional toxin domain eg. PE. In a preferred embodiment, the second ligand binding moiety binds to a ligand that is expressed primarily on a non-diseased cell type located in the bone marrow (eg. a stem cell, adipocyte etc.) and the first ligand binding moiety binds to a target ligand that is over-expressed on the offending cancer cell type. In this connection the invention is also directed to a method of relieving bone pain. The invention is also directed to combination therapies with this multispecific ligand, including immunotoxins, therapies with other multispecific ligands herein described and therapies directed at interfering with the integrity of tumor cell vasculature.

With respect to each of the preceding aspects of the invention, the invention also contemplates that the second ligand binding moiety is constituted by a ligand which binds to a bioresponse modifier (such as a cytokine, chemokine; growth factor etc. or related regulatory molecules such as inhibitors, agonists, antagonists of same, which have corresponding biological receptors), the ligand optionally having a higher affinity for the bioresponse

modifier than the affinity of that bioresponse modifier for its receptor, and wherein the ligand, combined with the bioresponse modifier (ie. bound thereto), has a relatively diminished ability to bind and/or stay bound to the receptor (the second target ligand) independently of the binding of the first target binding moiety to the first target ligand. The invention contemplates that the foregoing construct can be used to deliver the bioresponse modifier more selectively to the target cell population recognized by the first ligand binding moiety. The second ligand binding moiety may be the Fab portion of a multispecific ligand of the invention and the invention contemplates that a library of second ligand binding moieties, for example in the form of disassociated Fabs, recognizing multiple different epitopes on the bioresponse modifier, can be screened for their ability to bind to the bioresponse modifier, while bound in situ to its receptor, for example, using a microarrary of such Fabs, and the affinities of the binders can be evaluated. The invention also contemplates that suitable Fabs could be generated by "panning" (with an expression library, eg. phage display, ribosome display, or other similar display systems including yeast, bacterial, viral, cell based or cell-free display systems) or otherwise screening (eg. using antibody microarrays) against the bioresponse modifier while bound to its receptor and screening for their ability to bind to the bioresponse modifier independently of its receptor. Again, the affinities of the Fab-bioresponse modifier for the target receptor could be evaluated. More generally, the invention contemplates that an array of Fabs which recognize all different epitopes on a given bioresponse modifier could be generated and tested for their ability to accommodate binding of a bioresponse modifier to a first but not a second in a related family of receptors. This could be accomplished by screening the array for one or more members that bind to the bioresponse modifier (BRM) while bound to its receptor, and testing the identified members for their ability to bind to the second receptor, preferably by loading the bioresponse modifier onto an array of those members pre-bound with BRM and detecting those BRM bound members for those which do and do not bind to the second receptor. Therefore the invention is also directed to an antibody which accommodates binding of the BRM to one receptor but hinders the binding to at least one second receptor, preferably by steric, charge or other inter-molecular hindrance, attributable to the proximity of the antibody epitope on the BRM to the BRM's receptor binding site and optionally also the amino acid composition of the antibody at that interface.

The invention contemplates that fluid flow can be simulated in a purification or immunoaffinity column packed with one or more known packing materials to simulate flow over a ligand coated substrate.

The invention also contemplates an apparatus and method for testing ligand binding in a circulating fluid environment in which the multispecific ligands of the invention can be tested and wherein a continous flow of ligands, including target ligands, ligands of the invention and/or ligand bearing entities (eg. cells or synthetic eg. latex spheres which can be adjusted to a cell size) to which one or types of ligands have been affixedly associated accordingly to known methods) can be generated. The fluid contact interface of the apparatus has a generally circular shape and is convex or otherwise capable of containing the fluid and thereby preferably permits fluid to flow around the surface continuously. For example, this surface may be enclosed with a bagel-shaped cylinder which is optionally open at a location opposite the fluid contact surface for introducing and/or removing its contents, or it may completely enclosed with the exception of an access port, from which any air may optionally be displaced or evacuated. The invention contemplates that the apparatus (at least the fluid contact vessel) can be rotated or oscillated (eg. in an elliptical, oval or similar shape well known to those skilled in the arts of fluid mechanics and related engineering arts) in a variety of different planes or with rocking-like motion in multiple planes or subject to peristaltic pressure (ie. where flexible tubing is used) to generate a continuous, preferably turbulence free fluid flow over the fluid contact surface at selected rates simulating the various shear rates of arterial, venous, intra-lymphatic flow (including different diameters of such vessels) or interstitial flow. The invention also contemplates that the fluid contact surface may be provided with a 1) substrate for linking ligands of the invention or target ligands or ligand bearing entities to permit fluid flow across the substrate in a plane substantially parallel or conforming to the axis of flow and/or 2) optionally with one or more micro-screens or otherwise permeable substrates (eg. a loose network or matrix of bead-like materials or spheroids eg.latex spheres having associated ligands or purification column packing materials, optionally buoyant materials, or composite materials including a smaller bead serving as a spacer, or materials comprising projections or interconnections serving as spacers, so as to at least partially simulate flow around cells within a tissue) which are arranged transversely across the fluid path and at least partially intersect that path (see Figure _), the micro-screens optionally being impervious to the ligand-bearing entities eg. cells but not to the ligands eg. multispecific ligands of the invention (being tested for their binding ability)

In another aspect the invention is directed to methods of making a multispecific antibody in which:

a) the heavy chains are linked by a flexible linker such as $(sergly_4)_n$ to ensure that they are correctly linked (have different specificities) and the light chains are the same for both the VL domains (see Figures A & B). For example, the light chains (assuming the construct has two light chains) are generated for a first target binding moiety eg. in one aspect of the invention, the relatively high affinity binder, optionally from a light chain germline sequence, and this light chain is then coupled with a diversity of heavy chains to select a pair of chains which bind to the second target ligand, thereby constituting the second ligand binding moiety, which may be a relatively low affinity binder. An alternate or concomitant strategy to generate a lower affinity second ligand binding moiety would simply be to substitute the light chain of the first ligand binding moiety for that of the second ligand binding moiety and to test the affinity. In the case of a multispecific which target BRMs to particular target cells, where for example, two high affinity binders are preferred, the heavy chain and light chain binding to the BRM can be truncated

correspondingly at the CH1/CL region so that the VH/VL interfaces and cysteines pairing these heavy and light chains are similarly spaced but spaced differently from the other VH/VL chains. By linking the heavy chains as explained above, all chains will pair correctly. It will be appreciated that the foregoing production strategies could be applied to the production of heavy chain antibodies (two chains structures without associated light chains), wherein the heavy chains are from human or other species and that production in this case could be adapted to E. Coli. It will also be appreciated that deletion of a substantial part of the CH1 and CL domains can be measured to provide a space for the BRM to sit in line with the other Fab which can be lengthened in the linker or CH1 domain, as shown in Figure C. The invention contemplates that evaluation of a diversity of the first target binding moiety can be accomplished with the BRM place to best accommodate selection in the context of the entire structure as a whole.

b) With respect to other methods to make bispecific and bispecific fusions see Antibody Fusion Proteins Wiley-Liss 1999 (infra) eg. particularly p 131 et seq., Chapter 7,

Such a construct could also be employed in conjunction with other functional moieties fused or conjugated thereto, for example toxins, cytokines, enzymes, prodrugs, radionuclides etc.

In one preferred embodiment, the invention is directed to a multispecific ligand* with at least two different binding specificities for different target ligands* on the same target cell* and adapted to bind simultaneously to the different target ligands, said multispecific ligand comprising a first target binding moiety which preferentially* recognizes a first target ligand and a second target binding moiety which preferentially recognizes a second target ligand, and wherein said first target binding moiety recognizes a target cell-associated* target ligand and said second target binding moiety recognizes a non-cell-associated target ligand which is present on target cells and non-target cells; and wherein the ability of the second target binding moiety to bind to the second target is diminished relative the ability of the first target binding moiety to bind to the first target ligand, the first target binding moiety having an ability to bind to the first target ligand which is at least sufficient for the first target moiety to bind to the first target ligand independently of the second target binding moiety binding to the second target ligand and an off-rate which at least sufficiently exceeds the on-rate of the second target binding moiety for the second target ligand to provide opportunity for the second target moiety to bind the second target ligand when the first target binding moiety is bound to first target ligand, the second target binding moiety having a relatively diminished ability to bind or stay bound to the second target ligand independently of the binding of the first target binding moiety to the first target ligand, such that the multifunctional ligand will bind to the target population of cells in preference to the non-target population of cells. As suggested above, the strategy embodied in this preferred embodiment can also be employed in connection with any one or any combination of compatible strategies referred to above, to diminish the requirement of using a low affinity second ligand binding moiety.

In another aspect the invention is directed to heterofunctional ligand comprising a first moiety which binds to a first target ligand and a second moiety which binds to a second target ligand, and wherein the affinity or avidity or both the affinity and avidity of said first moiety are selected to enable the first moiety to bind to the first target ligand independently of the ability of said second moiety to bind to the second target ligand and wherein the relative avidity or affinity or both the affinity and avidity of said second moiety are selected or adjusted to substantially reduce the probability of the second moiety binding to the second target ligand without the first moiety, first or substantially contemporaneously, binding to the first target ligand. For example, in one embodiment the first moiety is divalent and the second moiety is monovalent. In one embodiment the affinity of the first moiety for its target ligand is for example up to several orders of magnitude greater than the affinity of the second moiety for its target ligand, as discussed below. In a preferred embodiment both moieties are capable of binding to different target ligands on the same cell, for example as hereinafter specified, although in the case of tumor cell targeting, particularly with respect to cells that are growing adjacent to another the invention contemplates that the first moiety may bind to one cell and the second moiety may bind to a neighbouring cell. Accordingly, in the case of receptors requiring cross-linking for biological activity the invention contemplates that such same cell interactions and adjacent cell interactions are optionally accomplished when the second moiety is bivalent. In one embodiment, at least one of said first and second moities comprise one or more antibody components. In another embodiment, said first moiety binds to at least one cell-surface ligand which differentiates between cells of the same population or sub-population, for example, at least one ligand which differentiates which between populations or sub-populations of immune cells (eg. see WO 01/21641, US 6156878), for example, activated vs. non-activated, disease-associated or non-disease-associated (over-expressing or uniquely expressing certain receptors or other ligands [for example cytokine or growth factor receptors, particular immunoglobulin like molecules or MHC peptide complexes] or other differentiating markers hereinafter exemplified or apparent to those skilled in the art), and said second moiety, in virtue of its binding to the second target ligand, directly or indirectly exerts a therapeutic effect, for example an immune modulating effect. In a further preferred embodiment said second moiety has a broader target cell population than said first moiety Eg. see Wiley H. et al. Expression of CC Chemokine Receptor-7 and Lymph Node Metastasis..., J. Natl. Cancer Inst. 93:1638-1643; Moore MA Bioessays 2001 Aug;23(8):674-6[10]. For example, in one embodiment said first moiety binds to a tumor associated antigen on a tumor cell and said second

[10] The invention contemplates that by targeting CCR7 receptor selectively on tumor cells, for example using a relatively high affinity binding moiety for a tumor associated antigen and a relatively low affinity moiety which binds to and blocks CCR7 receptor, eg. when combined with an immunotoxin for the same tumor, metastasis can be inhibited.

moiety binds to a receptor which is found on the tumor cell but also on a broader population of cells. In another embodiment said first moiety binds to an antigen associated with particular population of leukocytes and said second moiety binds to a receptor which is found on that population of cells but also on a broader population of cells (eg. apoptosis mediating receptors Journal of Immunology 1998 160:3-6, Nat Med 2001 Aug; 7(8)954-960, WO 01/85782; ICAM-R WO 00/29020; see also WO 01/85768, WO 01/85908; WO 01/83755, WO 01/83560, WO 01/29020; Vitale et al. Prpc. Nat. Acad. Sci. 2001 May 8; 98(10):5754-5769; CCR2 see also USP 6312689; USP 6,294,655 Anti-interleukin-1 receptor antagonist antibodies and uses thereof; USP 6,262,239; USP 6,268,477) . In another embodiment the second moiety does not necessarily bind with lower affinity to its target however it may bind to a first ligand which in turn binds to a second ligand on a target cell (eg. a receptor on the target cell eg. a cytokine, chemokine or growth factor receptor), for example the receptor being on the same cell to which he first moiety binds, and it binds in a manner in which it partially interferes with the binding of the first ligand to the second ligand and thereby directs or retargets that first ligand to the second ligand in a manner which accomplishes the intended interaction of the the first with the second ligand (eg a signal transduction or blocking interaction ie. the second moiety causes the eg. cytokine to bind to its receptor without engendering the biological effects attributable to receptor binding eg. signal transduction, which may be assessed by assaying for effects of eg. signal transduction according to well established techniques in the art) but less competitively relative to the first moiety so that the first moiety exerts a targeting function ie. where the first ligand bound by the second moiety binds to a broader than desired population of cells. The binding of the second moiety may also be compatible with the first ligand binding to one cell surface ligand but not another eg. see WO 00/64946 the contents of which are hereby incorporated by reference. The ability to identify ligand residues of importance to binding or residues other these, the alteration of which might interfere with binding is well established in the art. The invention contemplates varying, by high throughput techniques eg. phage display, residues of an antibody that are not involved in first ligand binding to create variants which can be tested for partial interference with first ligand binding to the second ligand eg. receptor binding.

Examples of receptors for blocking or activation by the targeting methods described herein include tyrosine kinase type receptors, serine kinase type receptors, heterotrimeric G-protein coupled receptors, receptors bound to tyrosine kinase, TNF family receptors, notch family receptors, guanylate cyclase types, tyrosine phosphatase types, adhesion receptors etc. (for example receptors see those discussed in Cancer: Principles and Practice of Oncology 6th Ed. De Vita et al. Eds Lippincott 2001, including particularly Chapter 3, 7 and 18, The Autoimmune Diseases, Academic Press Third Edition, Rose/Mackay ISBN: 0126969236, Immunology 6th Edition, Mosby 2001 Roitt et al. Eds; Molecular Mimicry, Microbes & Autoimmunity by Madeleine W. Cunningham (Editor), Robert S. Fujinami (Editor) December 2000, among other references hereininbelow identified). Further mention may also be made of interleukin and interferon type receptors, HGF receptor (see for example USP 6,214,344), CD45, CXC family receptors including CXCR1 and CXCR2 receptors including IL-8 receptor, EGFRs, receptors for molecules with functions in apoptosis or homeostasis, receptors such as FGF which sensitize tumor cells to chemotherapeutic agents, etc. It is known for example to modify receptor ligands in a way which does not interfere with a signaling function (the residues important for signaling may be known or can be readly ascertained eg. see Retargeting interleukin 13 for radioimmunodetection and radioimmunotherapy of human high-grade gliomas. Debinski W, Thompson JP.Clin Cancer Res 1999 Oct;5(10 Suppl):3143s-3147s) but reduces the affinity of the ligand for this receptor (see also WO 01/19861. Alternatively, the second moiety may be an antibody which is agonistic or antagonistic and used to block, activate, neutralize etc the receptor. With respect to EGFR family,TNF family and other receptor targeting antibodies which are capable of causing apoptosis directly or indirectly, see US 5,876,158, WO 00/20576, WO96/08515, WO 01/44808 (P75AIRM1), WO 00/29020 (ICAM-R), WO 99/12973, CA 2236913 etc. The invention also contemplates that the second moiety may also be targeted to a specific portion of a receptor which differentiates it from other receptors of its class and more generally contemplates that the second moiety may contribute to the targeting ability of the multifunctional ligand.

In another aspect, the invention also contemplates that the first moiety binds to a target cell and said second moiety binds to a ligand, for example a natural ligand, (eg. a cytokine or chemokine circulating at normal levels or at higher levels attributable to a disease or treatment of a disease with another therapeutic molecule) and retargets that ligand (for example, the ligand may be retargetted from circulation) to a targeted cell. For example the invention contemplates that IL-2 may be retargeted to LAK cells or CTLs via a high affinity Leu-19 binding first moiety. For example, antibodies including fragments thereof which bind to cytokines or other natural ligands for retargeting purposes (eg. single domain antibodies) can be made by phage display against the cytokine or ligand while bound in situ to its receptor. The invention also contemplates that the affinity for the cytokine may be adjusted to regulate the degree of targeting and that serum samples may be evaluated to assess the degree of bound cytokine and the relative degree of bound and unbound cytokine. Among other methods, for example, the invention contemplates that a radiolabelled multifunctional ligand may be used assess the amount of label associated with the multifunctional ligand when bound to the cytokine, by capturing the 'complex' with an antibody that recognizes both antigenic determinants on both the cytokine and an adjacent portion of the ligand binding thereto ie. forming a composite epitope), such as may be generated by phage display and assessing the amount of label relative to the amount of captured complex.The invention also contemplates administration of supplemental amounts of natural ligand to compensate for the degree in which the ligand is retargeted insofar as such retargeting might impact negatively on immune or other physiological processes.

In another aspect the invention contemplates that patients treated with antibodies to a particular natural ligand eg. a cytokine, for example TNFα, may preferably be treated with a multifunctional ligand having a first moiety which binds to at least one tumor type and a second moiety which binds to a natural ligand such as a cytokine for

retargeting that cytokine to tumor tissues, as in a preventative method for treating cancer. In this respect the invention contemplates that the antibody is capable of binding to the cytokine but once bound the cytokine, the cytokine is incapable and/or only weakly capable of binding to its receptor and/or that the multifunctional ligand also comprises a higher affinity receptor blocking moiety to minimize retargeting of the primary disease site. In one embodiment, the first moiety binds with relatively higher functional affinity (ie. avidity, affinity, and/or relatively advantageous binding capacity in virtue of multiple ligand binding arms, each binding to different ligands on the target cell) to ensure binding to the retarget cell. In another embodiment the bound cytokine is capable of binding to the cytokine receptor at the retarget site but incapable of binding to the receptor at the disease site owing to differences in the receptors at the two sites.

For example, patients with Crohn's disease that are treated with anti-TNFα (see for example, Expert Opin Pharmacother 2000 May;1(4):615-22 and references cited therein) may be treated according to the invention with a bispecific antibody having, in addition to an anti-TNFα binding moiety, which reduces the affinity of the bound TNF for the receptor, but also an antibody moiety which binds to tumor antigen which is expressed on many different tumor types or optionally a trispecific antibody which additionally binds to a second multi-carcinomic antigen, preferably one which broadens the range of targeting against prevalent cancers. With respect to tumor antigens mention may be made of EGFR, EPCAM, MUCINs, TAG-72, CEA, H11 among other known multicarcinomic antigens (see also Cancer: Principles and Practice of Oncology 6th Ed. De Vita et al. Eds Lippincott 2001 Chapters 18 and 20.5). In another embodiment, the second moiety differentially retargets a cytokine to one receptor in preference to another, for example, to a TNF receptor over-expressed on tumor cells in preference to a TNF receptor associated with Crohns disease. In a related but also independent aspect, the invention contemplates a method of screening for an antibody which preferentially binds to a ligand when bound to a first receptor relative to another second receptor by screening for antibodies (eg. by phage display, ribosome display, etc.) which bind to the ligand eg. a cytokine, when bound in situ to the first receptor, and selecting among them those that bind to the ligand eg. cytokine but do not bind (substractive screening) or bind with lesser affinity to the cytokine when bound to the second receptor, as well as to antibodies and multifunctional ligands created by this method (see also USP 6,046,048 and WO 99/12973 and references cited therein with respect to TNF family of receptors). Variations in the extracellular domains of such receptors are known and can be ascertained by methods known to those skilled in the art.

Further with respect to multifunctional ligands having a higher affinity targeting moiety relative to the second ie. effector moiety, the second moiety may be for example an antibody or other ligand which interferes with the binding of the regular ligand for this receptor. For example, the invention contemplates a first ligand binding moiety which recognizes activated T-cells and a second ligand binding moiety which blocks the IL-16 receptor for testing the effect on Crohns disease (or alternatively activates an IL-16 receptor on those cells eg. by using a high affinity IL-16 bound second moiety which becomes relatively low affinity IL-16 receptor ligand when bound to the antibody, again to test the effect on Crohn's disease (see Gut 2001 Dec. 49(6) 795-803) For example, in one embodiment, the invention contemplates that the second moiety blocks a receptor that are found on cells other than the target cell, the blockage of which leads to the apoptosis of or destruction of the cell eg. CD95 (eg. see Jung G. et al.,Target cell-restricted triggering of the CD95 (APO-1/Fas) death receptor with bispecific antibody fragments Cancer Res 2001 Mar 1;61(5):1846-8). With respect to blocking insulin like growth factor receptor, insulin receptor etc. see The IGF system in thyroid cancer: new concepts. Vella V., Mol Pathol 2001 Jun;54(3):121-4; Insulin receptor isoform A, a newly recognized, high-affinity insulin-like growth factor II receptor in fetal and cancer cells. Mol Cell Biol 1999 May;19(5):3278-88; Expression of the insulin-like growth factors and their receptors in adenocarcinoma of the colon. Freier S Gut 1999 May;44(5):704-8; Pandini G., Insulin and insulin-like growth factor-I (IGF-I) receptor overexpression in breast cancers leads to insulin/IGF-I hybrid receptor overexpression: evidence for a second mechanism of IGF-I signaling.Clin Cancer Res 1999 Jul;5(7):1935-44. With respect to targeting beta-1 integrins see eg. Masumoto A, Arao S, Otsuki M. Role of beta1 integrins in adhesion and invasion of hepatocellular carcinoma cells.Hepatology. 1999 Jan;29(1):68-74.Arao S, Masumoto A, Otsuki M.Beta1 integrins play an essential role in adhesion and invasion of pancreatic carcinoma cells.Pancreas. 2000 Mar;20(2):129-37. Xie Y, Xie H.Characterization of a novel monoclonal antibody raised against human hepatocellular carcinoma.Hybridoma. 1998 Oct;17(5):437-44.Peng H, Cao Z, Zhou S, Wang Z, Lei B, Zhao L.[Production and characterization of anti-human hepatocellular carcinoma monoclonal antibodies].Hua Xi Yi Ke Da Xue Xue Bao. 1990 Sep;21(3):259-62; Whittard JD, Akiyama SK.Activation of beta1 integrins induces cell-cell adhesion.Exp Cell Res. 2001 Feb 1;263(1):65-76 Nejjari M, Hafdi Z, Dumortier J, Bringuier AF, Feldmann G, Scoazec JY.alpha6beta1 integrin expression in hepatocarcinoma cells: regulation and role in cell adhesion and migration.Int J Cancer. 1999 Nov 12;83(4):518-25; Yao M, Zhou XD, Zhe XL, Shi DR, Fu J, He JY, Lu HF, Tang ZY.Expression of the integrin alpha5 subunit and its mediated cell adhesion in hepatocellular carcinoma. J Cancer Res Clin Oncol. 1997;123(8):435-40.

The invention also contemplates a method of optimizing the cooperative affinities of respective binding ligands of a multifunctional ligand described herein and the length of a linker therebetween for the above and applications described below by phage or ribosome display etc; in which the multifunctional ligand is a single polypeptide chain, for example, two single chain Fvs or single domain antibodies linked in sequence, or a diabody (see USP 5,837,242), by varying the DNA sequence corresponding to amino acids that represent linker and/or for example CDR regions that are postulated to impact on affinity according to methods and strategies that well known in the art for affinity maturation. These same strategies can be employed for engineering lower affinity molecules. Accordingly, more generally the invention is directed to a phage display or similar library (eg. a ribosome display

library or a microarray) in which the population of variants is a multifunctional ligand, including a multifunctional ligand according to the invention herein defined.

In another embodiment blockage of a receptor does not necessarily lead to cell death but may lead only to decreased or increased release of certain cytokines etc, for example as mediated via the IL-6 receptor. In another embodiment the second moiety may achieve the desired therapeutic effect by constituting the normal ligand for that receptor or a functional substitute. The heterofunctional ligand may also be fused or conjugated to a toxic moiety or other effector. In another or further preferred embodiment, said first moiety comprises two binding ligands (eg. one or both of which may be an antibody) which respectively bind to two different target ligands each of which contributes to its total binding capacity and neither of which are sufficient to efficiently target the the cell, for example a ligand which binds to a specific MHC peptide complex and a second reduced affinity ligand which binds to a ligand on an APC. This approach also obviates the need to create high affinity ligand for a particular MHC petide complex, although this can been accomplished. In another or further preferred embodiment the target cell is an immune cell and the second moiety binds to a molecule involved in cellular adhesion, a cytokine receptor, a ligand which stimulates the activity of said immune cell, a ligand which inhibits the activity of said immune cell, a ligand which causes one or more cytokines to be released, a ligand which prevent one or more cytokines from being released, a ligand which causes or facilitates apoptosis of said immune cell or a ligand which permits internalization of said heterofunctional ligand. In another preferred embodiment the heterofunctional ligand is fused or conjugated to a therapeutic agent or a moiety that binds to a therapeutuc agent (exemplified below) or a ligand which effects binding to another immune cell, for example a T cell. In another preferred embodiment, the heterofunctional ligand is a bispecific antibody, a trispecfic antibody or a tetraspecific antibody. In a further preferred embodiment the first moiety binds to but is incapable of modulating the activity of said immune cell and said second moiety modulates the activity of said immune cell independently of said first moiety. In another preferred embodiment the heterofunctional ligand further comprises a moiety that binds to at least one ligand located on the intraluminal surface of a lymphatic vessel, preferably a lymphatic vessel associated ligand, as hereinafter defined. In other aspects the invention is directed to a pharmaceutical composition comprising such a heterofunctional ligand and a pharmaceutically acceptable carrier, a method of using the heterofunctional ligand in the preparation of a pharmaceutical composition for treating a disease, and to a method of treating a subject by administering same in a therapeutically effective amount.

The term heterofunctional is used broadly to refer to a ligand: 1) comprising at least two functional moieties that have different functions or different capacities to perform the same function and 2) which is typically and preferably heterospecific (having two binding specificities).

Unless the context dictates otherwise the term avidity when used in a comparative, quantifiable or controllable sense is used to refer the valency of the binding entity or moiety. The term functional affinity is used a composite term referring to a quantitative and controllable (though not necessarily quantifiable, especially when its consists of both avidity and affinity components) propensity to specific binding attributable to one or both of avidity and affinity effects.

In another aspect, the invention contemplates that cells, particularly immune cells, that are expected to be present at or proximal to a disease site (eg. at the site where an immune cell crosses the vascular endothelial cell wall), in virtue of the disease or a therapeutic modality which is employed in relation to the disease or a concurrent disease, excluding cells that directly mediate the disease, may be targetted in virtue of a marker associated with such cells, eg. LEU-19, a marker associated with activated or killerT-cells, etc for example with an antibody, which is linked to a moiety that is capable of exerting a therapeutic effect in relation to the disease, for example, an immunoliposome or an antibody linked to another therapeutic delivery system (for example example streptavidin or biotin fused, coated or conjugated entities or other payload carrying entities (see for example US patents 5439686, 6007845, 5879712, 5456917, 6165502, 5079005, 5888500, 5861159, 6193970, 6190692, 6,077, 499, WO 00/69413, WO 01/07084, etc.). For example, an immunoliposome may carry one of or a combination of cytokines, chemokines, toxins or other therapeutic molecules suitable for treating the disease directly or indirectly, for example by attracting or preventing the attraction, activating, anergizing or otherwise modulating the activity of immune cells for therapeutic or related purposes.

In another aspect the invention is directed to a heterofunctional ligand comprising a first moiety which specifically binds to at least a first target ligand on a first entity and a second moiety which specifically binds to at least a second target ligand on a second entity, and wherein the affinity or avidity or both the affinity and avidity of said first moiety are selected to enable the first moiety to bind to the at least one first target ligand independently of the ability of said second moiety to bind to the at least one second target ligand and wherein the avidity or affinity or both the affinity and avidity of said second moiety are selected to enable the second moiety to bind to the second entity in preference to the first moiety binding to the first entity when both first and second moieties are substantially contemporaneously bound to the respective first and second entities. In one embodiment the first moiety comprises at least one ligand preferably at least one antibody which binds to a first cell, for example an intraluminal lymphatic endothelial cell and the second moiety comprises a ligand, preferably at least one antibody which binds to a different cell, for example a disease associated cell (hereinafter exemplified and meaning, unless the context implies otherwise, diseased cells or disease causing, mediating (ie. having a role which is known to be intermediary or indirectly facilitating eg. antigen presenting cells) or mitigating cells (cells, typically immune cells,

which directly or indirectly counteract the diseased or disease causing or mediating cells). In other aspects the invention is directed to a pharmaceutical composition comprising such a heterofunctional ligand and a pharmaceutically acceptable carrier, a method of using the heterofunctional ligand in the preparation of a pharmaceutical composition for treating a disease, and to a method of treating a subject by administering same in a therapeutically effective amount.

In another aspect the invention is directed to a heterofunctional ligand comprising a first moiety which specifically binds to at least one first target ligand on a first entity and a second moiety which specifically binds to a second target ligand or site on a second entity, and wherein the second entity binds to a third target ligand, and wherein the first and third target ligands may be on the same or different entities eg. the same or different cells, and wherein preferably the affinity or avidity or both the affinity and avidity of said first moiety are selected to enable the first moiety to bind to the first target ligand independently of the ability of said second moiety to bind to the second target ligand and independently of the ability of the second moiety to bind to the third target ligand (the first moiety optionally comprising more than one ligand (which may be the same ligand or a different ligand) one or more of which are necessary for binding and optionally each of which is sufficient for specific binding) to corresponding first target ligands) and preferably wherein 1) the avidity or affinity or both the affinity and avidity of said first moiety is/are selected to enable it to bind to the at least first target ligand in preference to the second moiety binding to the third target ligand when both said first and second moieties and the second entity are substantially contemporaneously bound to their respective target ligands eg. to effect a tranfer or 2) wherein the avidity or affinity or both the affinity and avidity of said second moiety for the second entity are selected to enable the first moiety to bind to the first entity in preference to the second moiety binding to the second entity and/or 3) wherein the avidity or affinity or both the affinity and avidity of said second moiety for the second entity are selected to enable the second moiety to bind to the third target ligand in preference to the second moiety binding the second entity when both first and second moieties are substantially contemporaneously bound to the respective first and second entities and the second moiety is substantially comtemporaneously bound to the third target ligand), or 4) wherein both 1) and 2) above are both operative conditions. In one embodiment, the first entity is a diseased or disease causing, mediating or mitigating cell, for example an immune cell (the first moiety preferably binding to a particular population or sub-population of the first target entity eg. the immune cell, for example activated T cells), the first moiety optionally comprising two or more ligands which may be the same or different and which bind to two or more respective first target cell surface ligands (though not necessarily to any particular effect (and in one embodiment to no effect at all) ***other than*** to better bind to and thereby target the cell, preferably in competition with the second entity, which in a preferred embodiment targets a broader population of cells), and the second entity is an entity that binds to a third target ligand, the third target ligand preferably being expressed on the surface of a cell for example the same immune cell, for example a natural cell surface ligand, to which binding yields a desired effect, for example a therapeutic advantage, the second moiety being, for example, the natural ligand for the cell surface ligand or functional mimitope or antagonist or agonist thereof, for example a cytokine, the third target ligand in this case being a cytokine receptor on the immune cell. The invention is also directed to a method of "targeted delivery" of a therapeutic entity to a cell in need of such therapy by administering said heterofunctional ligand. In this respect numerous therapeutic entities will be apparent to those skilled in the art, only some of which are mentioned herein by referring to the therapeutic entity itself or by referring to the third target ligand for which such entity is known and available or readily made by routine skill in the art. Optionally the heterofunctional ligand is delivered with the second entity, preferably in the same composition (preferably bound). In the case where the second entity is a natural ligand circulating in the path of delivery of the heterofunctional ligand, some proportion (0-100%) of the heterofunctional ligand may be delivered without supplied second entity, particularly if the treatment or the disease generates an abundance of the natural ligand. In another embodiment the first moiety binds to a target ligand on a stationary cell (for example a vascular endothelial cell or a lymphatic endothelial cell), preferably a tissue or cell type "associated" ligand (more abundantly expressed uniquely expressed on target cells relative to non-target cells), and the third target ligand and the second moiety are cell-suface target and ligand therefor as stated above, for example the second moiety binds to a cytokine and the third target ligand is a cytokine receptor, for example on an immune cell. In one embodiment the first moiety binds to at least one target ligand which differentiates between populations or sub-populations of immune cells and the second entityty in virtue of its binding to the third target ligand, directly or indirectly exerts a therapeutic effect, for example by modulating the activity of said immune cell. In another or further preferred embodiment the first moiety is incapable of modulating the activity of said immune cell and said second entity modulates the activity of said immune cell independently of said first moiety. In another or further preferred embodiment the second entity binds to a molecule involved in cellular adhesion, a cytokine receptor, a ligand which stimulates the activity of said immune cell, a ligand which inhibits the activity of said immune cell (eg. via anergy or tolerance mechanisms), a ligand which causes one or more cytokines to be released, a ligand which prevent one or more cytokines from being released, a ligand which causes or facilitates apoptosis of said immune celll, a ligand which permits internalization of said heterofunctional ligand. In another preferred embodiment the heterofunctional ligand is fused or conjugated to a therapeutic agent or a moiety (eg. biotin, avidin) that binds to a therapeutuc agent (exemplified below) or a ligand which effects binding to another immune cell, for example a T cell. In another preferred embodiment, the heterofunctional ligand is a bispecific antibody, a trispecfic antibody or a tetraspecific antibody. In another preferred embodiment the heterofunctional ligand further comprises a moiety that binds to at least one ligand located on the intraluminal surface of a lymphatic vessel, preferably a lymphatic vessel associated ligand, as hereinafter defined.

In other aspects the invention is directed to a pharmaceutical composition comprising such aforementioned heterofunctional ligand and a pharmaceutically acceptable carrier, a method of using the heterofunctional ligand in the preparation of a pharmaceutical composition for treating a disease, and to a method of treating a subject by

administering same in a therapeutically effective amount. As suggested below, the foregoing strategy could be used in combination with other targeting strategies herein mentioned or known in the art. The invention contemplates making antibodies to second entities, for example, while bound to their natural receptor, by phage or ribosome display, by methods as hereinafter disclosed.

In another aspect the invention is directed to a heterofunctional ligand comprising at least a first moiety which specifically binds to a first target ligand on a cell and a second moiety which specifically binds to at least a second target ligand on the same cell, and wherein the affinity or avidity or both the affinity and avidity of said first moiety and the affinity or avidity or both the affinity and avidity of the second moiety are selected to substantially reduce the probability of the either moiety singly binding to its respective ligand for a sufficient duration or series of durations to accomplish the function of said heterofunctional ligand unless both first and second moieties are substantially contemporaneously bound to the cell. In a preferred embodiment the first moiety binds to at least one target ligand which differentiates between populations or sub-populations of immune cells and the second moiety in virtue of its binding to the second target ligand, directly or indirectly exerts a therapeutic effect, for example by modulating the activity of said immune cell. In another or further preferred embodiment the first moiety is incapable of modulating the activity of said immune cell and said second moiety modulates the activity of said immune cell independently of said first moiety. In another or further preferred embodiment the second moiety binds to a molecule involved in cellular adhesion, a cytokine receptor, a ligand which stimulates the activity of said immune cell, a ligand which inhibits the activity of said immune cell (eg. via anergy or tolerance mechanisms), a ligand which causes one or more cytokines to be released, a ligand which prevent one or more cytokines from being released, a ligand which causes or facilitates apoptosis of said immune cell, a ligand which permits internalization of said heterofunctional ligand. In another preferred embodiment the heterofunctional ligand is fused or conjugated to a therapeutic agent or a moiety (eg. biotin, avidin) that binds to a therapeutic agent (exemplified below) or a ligand which effects binding to another immune cell, for example a T cell. In another preferred embodiment, the heterofunctional ligand is a bispecific antibody, a trispecific antibody or a tetraspecific antibody. In another preferred embodiment the heterofunctional ligand further comprises a moiety that binds to at least one ligand located on the intraluminal surface of a lymphatic vessel, preferably a lymphatic vessel associated ligand, as hereinafter defined. In other aspects the invention is directed to a pharmaceutical composition comprising such a heterofunctional ligand and a pharmaceutically acceptable carrier, a method of using the heterofunctional ligand in the preparation of a pharmaceutical composition for treating a disease, and to a method of treating a subject by administering same in a therapeutically effective amount.

In other aspects the invention is directed to a method of in vivo modeling or testing using one or more foregoing targeting strategies by administering a heterofunctional / multifunctional ligand as hereinbelow disclosed as well as a method of intra-lymphatic drug delivery employing such ligand and such strategies including adaptations thereof for such purposes, as hereinafter described. In related aspects the invention is directed to a test ligand in the form of such a heterofunctional / multifunctional ligand and compositions thereof.

In one aspect, the invention is directed to a heterofunctional ligand, comprising a first moiety which specifically binds to at least one ligand located on the intraluminal surface of a lymphatic vessel and a second moiety which specifically binds to a disease associated cell and the use of such heterofunctional ligand in treating or preparing a pharmaceutical composition for treating disease associated cells, including diseased cells or disease causing, mediating (ie. having a role which is known to be intermediary or indirectly facilitating eg. antigen presenting cells) or mitigating cells (cells, typically immune cells, which directly or indirectly counteract the diseased or disease causing or mediating cells), within a lymphatic vessel. Preferably, the ligand located on the intraluminal surface of a lymphatic vessel is a lymphatic vessel associated ligand.

In another aspect, the invention is directed to a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a heterofunctional ligand comprising a first moiety which specifically binds to a ligand located on the intraluminal surface of a lymphatic vessel and a second moiety which specifically binds to said disease associated cell and the use of such ligand in treating treating disease associated cells, including diseased cells or disease causing or mediating cells, within a lymphatic vessel. Preferably, the ligand located on the intraluminal surface of a lymphatic vessel is a lymphatic vessel associated ligand.

In another aspect, the invention is directed to a method of treating disease associated cells, including diseased cells or disease causing or mediating cells, within a lymphatic vessel comprising administering to a subject a heterofunctional ligand comprising a first moiety which specifically binds to a ligand located on the intraluminal surface of a lymphatic vessel and a second moiety which specifically binds to said disease associated cell.

It is to be understood that disease causing cells as used herein includes diseased cells and pathogens, including micro-organisms and viruses.

In another aspect, the invention is directed to a heterofunctional ligand, comprising a first moiety which specifically binds to at least one ligand located on the intraluminal surface of a lymphatic vessel and a second moiety which specifically binds to a therapeutic entity for example a cytotoxin or cytotoxin-linked-entity or a non-toxic entity which is present in toxic amounts and to a method of reducing the toxic effect of such entity in a subject by administering said heterofunctional ligand to said subject.

In another embodiment is directed to a method of therapeutic evaluation and/or targeting / intervention in which such heterofunctional ligand is administered substantially contemporaneously with a cytotoxic substance for example a cytotoxic substance useful for treatment of cancer. The term substantially contemporaneously is used in this connection to mean in a time frame that permits both to exert their respective effects, preferably one or both exerting their respective effect optimally, or one exerting its effect dominantly. It will be appreciated that this might entail that one such entity is advanced in its delivery over the other. Optionally, one or both of these cooperating entities are delivered proximally to their respective target cells, for example by cannulating one or more blood vessels as proximally as possible to the site(s) of a tumor and/or actual or anticipated site(s) of metastases (as discerned by using one or more tumor and vascular imaging agents, for example, one or a combination two or more agents selected from a vascular opaquing agent, a radionuclide conjugated anti-angiogenic antibody, and a radionuclide conjugated anti-vascular endothelial cell marker antibody, which cannulation may occur for example in the course of initial surgical intervention with respect to the primary tumor site) and/or at the same time cannulating one or more lymphatic vessels (which may optionally be located which the help of a radionuclide conjugated anti-lymphatic vessel marker antibody) leading to or from such tumor sites or metastases. The invention contemplates that small sections of vascular prostheses, well known to those skilled the art (eg. Dacron types) may be grafted into those locations to permit a prolonged and secure attachment of such prosthesis to an intra-vascular cannula for secure delivery to such vascular or lymphatic locations for repeated and/or prolonged administration, optionally while the patient is mobile, optionally using one or more portable infusion devices, including micropumps designed for such purpose (see for example J Neurosci Methods 1997 Mar;72(1):35-8, US 5180365:Implantable infusion device See also Cancer Principles and Practice (infra). Numerous embodiments and improvements in vascular prosthesis and in such portable infusion devices and micopumps are described in the relevant scientific and patent literature known to those skilled in the art. The invention also contemplates delivering any multifunctional ligand herein disclosed in the above manner.

It is to be understood that targeting strategies employing the cooperative action of ligands with different affinities for their targets exemplified above, may preferably have affinities which differ, depending on the application and their avidity, by a factor of 20% up to a number of orders of magnitude which may one, two, three, four, five, six and even seven or eight order of magnitude, in order to achieve substantial advantage, as herefter detailed in connection with one such strategy.

In another aspect the invention is directed to a heterospecific ligand comprising a first moiety which specifically binds to at least a first disease associated ligand located on a diseased or disease causing, mediating or mitigating cell for example a cancer cell or an immune cell, as well as on non- diseased or disease causing, mediating or mitigating cells (non-target cells) and at least a second moiety which specifically binds to a second different disease associated ligand on the same cell and wherein each ligand is expressed on a substantially (see definition below) different, preferably non-overlapping, subset of non-target cells, so that functional binding to a non-target tissue is substantially (see definition below) precluded. In another embodiment the functional affinities of the respective ligands may be selected in accordance with the strategies suggested above, to further facilitate targeting. In another embodiment, both different ligands are required for internalization. In other related embodiments, the heterofunctional ligand comprises at least two different pairs of binding moieties (eg. a trispecific or tetraspecific antibody which depending on its construction will permit 2, 3 or 4 such different pairs eg. a tetraspecific single domain type antibody (ie. consisting primarily of the heavy or light chain variable region or a functional fragment thereof) (see discussion below regarding its construction) allowing the greatest variation in such geometries and preferably simultaneous binding of more than one pair), wherein 1) at least three such ligands are expressed on a substantially (see definition below) different, preferably non-overlapping, subset of non-target cells, so as to further limit binding to non-target cells and/or 2) wherein at least two different pairs of ligands target a substantially different subset of cells within the same target population eg.different cells within the same tumor (eg. proliferating vs. non-proliferating cell – the respective amounts of the different types of cells will dictate the percentage of the dose that will be targeted to one population or another). n other aspects the invention is directed to a pharmaceutical composition comprising such a heterospecific ligand and a pharmaceutically acceptable carrier, a method of using the heterospecific ligand in the preparation of a pharmaceutical composition for treating a disease, and to a method of treating a subject by administering same in a therapeutically effective amount. It will be appreciated that the foregoing general strategy can be accomplished with two or more different antibodies have differing and preferably non-overlapping normal ie. non-targeted cell distributions, preferably administered in the same composition and preferably cross-linked by biotin-avidin like complementary pairs to facilitate cross-linking for internalization or targeting of therapeutic agents. In a preferred embodiment each such independent antibody carries a different complimentary aspect of a toxic payload eg. a different liposome (or other payload carrying entity for example a micro or nano particle or sphere or albumin) which complement each other in virtue of their respective contents (eg. one carries the prodrug and the other the necessary converting enzyme).

In another aspect, the invention is directed to a multifunctional ("multi" meaning at least two) ligand having, at least, a first portion which binds to a lymphatic vessel associated ligand and a second portion comprising an immune function-exerting moiety.

The term lymphatic vessel is used to facilitate broader reference to ligands (eg. antigens / receptors) present on cells bordering the intra-luminal pathway through the lymphatic system including preferably the lymphatic vessels and optionally also parts of the lymph nodes, and refers in the case of the lymphatic vessels, primarily (from a functional standpoint) to the intra-luminal cell surfaces (not necessarily to the exclusion of non-luminal surfaces) on

the intra-luminal endothelial cells (not necessarily to the exclusion of non-luminal lymphatic endothelial cells) of those vessels.

The term 'associated' with reference to lymphatic vessels, is used to mean differentially expressed on the surface of endothelial cells of those vessels for targeting purposes, such as to accomplish an object of the invention, but unless otherwise expressly indicated in a particular instance, it is used limitatively, to reference ligands that are predominantly, if not exclusively, found on the aforementioned endothelial cell surface (as well as in lymph nodes), such that the first portion of the multifunctional ligand is for all intents and purposes functionally targeted to the intra-luminal surface of the lymphatic system. For instance, it is appreciated that the ligand in question may be targetted to a limited extent elsewhere eg. in the case of preferred LYVE-1 ligand discussed below, to parts of the spleen (which also provides a venue for immune cell interactions).

The invention is not concerned with imparting effects to or simply blocking a receptor on the intraluminal lymphatic endothelial cell. In this context, the multifunctional ligand of the invention is intended to exclude only, unless otherwise specifically stated in the claims, only those embodiments disclosed in WO 98/06839 or other references describing ligands, antagonists or antibodies which bind to a lymphatic vessel associated ligand or receptor (see examples of such references below), insofar as such embodiments comprise lymphatic vessel associated ligands as hereinabove limitatively defined, and to this limited extent only, the term immune function exerting moiety preferably excludes: 1) an antibody *Fc receptor*, insofar as such limitation excludes from the scope of the multifunctional ligand (per se) aspects of the invention, substantially intact naked antibodies which simply bind to a lymphatic vessel associated ligands, as well as preferably excluding 2) *cytotoxins or drugs*, insofar as this excludes from the scope of the mutifunctional ligands of the invention an antibody or fragment thereof which is fused or conjugated etc. exclusively to a cytotoxic molecule (including an atom) or drug (ie. an antibody linked to a cytotoxin or drug only, which is not per se an or is not integrated with *an independent* immune function exerting component) so as to accomplish a function in relation to cells or other entities (including other multifunctional ligands) within the lymphatic other than the cell or ligand to which the multifunctional ligand is anchored.

In the same vein, the term immune function is broad in intent (as discussed below, and includes particularly any function, including binding, capable of being exerted by an ligand preferably an antibody (eg. multifunctional ligands which are bispecific antibodies) however it is to be understood that the invention and particularly the immune function exerting moiety does not have as an object (despite possible incidental effects) evaluating or exerting a disease responsive or immune function vis-à-vis ligands / cells lining the intra-luminal surface of the lymphatic system ie. insofar as such ligands have a role in disease (other than simple binding exclusively for anchoring purposes which is attributable not the immune funtion exerting moiety but to the first portion) *but rather*, as evident in preferred aspects of the invention, preferably an ***independent*** immune function which is not predicated on blocking the lymphatic endothelial receptor or treating cells bearing the receptor ie. exerted vis-à-vis targets other than the lymphatic endothelium target, for example 1) in the case of stationary diseased cells or disease causing cells or molecules, targets at the site of the disease (which may optionally be effected, for example, in case of immunization or other immune cell stimulation, inhibition etc. in the lymphatic system); and 2) in the case of non-stationary diseased or disease causing cells or molecules, at the site of those cells / molecules including, preferably, within the lymphatic system, for example by binding to or signaling those cells in the lymphatic system.

1. In one embodiment, the first portion of the multifunctional ligand is an antibody.

2. In another embodiment, the immune function exerting moiety binds to a target ligand and thereby directly or indirectly accomplishes its effect (in whole or part). For example, the target ligand may be a cytokine, for example in order to target immune cells to the lymphatic system to assist in, diseased, disease causing or other target cell ablation or phagocytic type activity (eg. by the cytokine in turn binding to a ligand, for example on an immune cell having phagocytic activity) or exerting a chemotactic effect within the lymphatic system, or to mop up cytokines, for example, when released in toxic amounts due, for example due to effects of a disease or particular immunotherapy (such as anti-CD3 therapy; see for example USP 6193969, Kummer U. et al., Immunol Lett 2001 Jan 1; 75(2):153-158) (with respect to removing disease associated antibodies from circulation see for example a bispecific dsDNAxmonoclonal antibody construct for clearance of anti-dsDNA IgG in systemic lupus erythematosus.J Immunol Methods. 2001 Feb 1; 248(1-2):125-138). (see also, for example, US 5,968,510 with respect to antibody-CTLA-4 fusion proteins for use in binding to various target ligands).

3. In another embodiment, said immune function exerting moiety comprises an antibody and optionally both the first portion and the immune function exerting moiety are antibodies (with respect to bispecific antibodies, and a recent review of some of the technologies referred to or applicable to the invention (see particularly, Journal of Immunological Methods February 2001 Vol. 248(1-2) page 1-200)

4. In another embodiment, said immune function exerting moiety binds to an immune cell, a diseased host cell or a disease causing cell or entity (eg see US6193968). The term disease is used broadly to refer to any undesirable condition. The term diseased host cell includes but is not limited to a cancerous (in the broadest sense of that term) cell and a virally infected cell (these examples are given inasmuch as the invention in a preferred embodiment involves targeting such cells for

destruction) and the term disease causing cell includes but is not limited to a virus or other infectious agent and as well as immune cell which is directly or indirectly involved in mediating or causing a undesired, deleterious or pathologic consequence, including but not limited to autoimmune disorders, transplant rejection, and other immune system linked diseases. The term disease causing entity is used to refer, without limitation, to any molecule, atom, peptide, ligand, complex, chemical, component, epitope etc. that is directly or indirectly involved or associated in mediating or causing a disease or disease causing event including an antibody. Such binding to the entity may be effected through the instrumentality of one or more (same or different) multifunctional ligands and through binding to any ligand or set of ligands, including receptors, multi-component epitopes etc, including for example, tumor *"associated"* (ie. differentially expressed to advantage for targeting purposes) epitopes which may or may not or may only be partially present on tumor associated antigens, or commonly, for example antigens / epitopes / ligands / receptors etc. which are over-expressed in association with cancer cells; or for example, antigens / epitopes / ligands / receptors etc. involved in immune signaling, stimulatory, co-stimulatory, inhibitory, adhesion or other interactions, including without limitation, cytokine receptors, ligands associated with immune cell adhesion (see for example US 5,747,035), ligands to which binding results in stimulation, activation, apoptosis, anergy or costimulation, or ligands which differentiate between different populations or subpopulations or immune cells, including sub-populations of B cells and T cells, activated versus non-activated lympocytes, diseased or disease-causing cells versus non-diseased / disease causing lymphocytes and specific immune cell clones for example those having specific Ig type and MHC-peptide type ligands / and correlative ligands. Examples of such ligands include CCR5, CTLA-4, LFA-1, LFA-3. ICAMs eg. ICAM-1, ELAM-1, CD2, CD3, CD4 (eg see US 6,136,310), CD5, CD6, CD18, CD22, CD40, CD44; CD80, CD86, CD134 and CD154, to name only a few (see also US6087475: PF4A receptor, US6135941, WO 01/13945A1:METHODS AND COMPOSITIONS FOR IMMUNOTHERAPY OF B CELL INVOLVEMENT IN PROMOTION OF A DISEASE CONDITION COMPRISING MULTIPLE SCLEROSIS).

5. The invention is also directed to a multifunctional ligand and a method which comprises using the multifunctional ligand to assess the toxicity of directly or indirectly targeting, for example, primarily within the lymphatic vessel system (see discussion below), cells having well known markers that are associated with immune cells, for example, those exclusively associated with activated immune cells, in-so-far as such targeting has a role in prolonging or counteracting the activated state, destroying the cell (eg. where the multifunctional ligand is a immunotoxin) causing the cell to be destroyed (eg. through apoptosis (eg. see WO 01/19861, fas – fasL, U.S 6,046,048) or assisting another molecule or cell for example a T-cell or other killing or immune modulating cell to do the modulation or killing (markers such as CD23, CD25, CD26, CD28, CD30, CD38, CD49a, CD69, CD70, are just some of the markers associated with activated immune cells) etc. (for a complete listing of marker associated with activated immune cells see for example Roitt I et al. Immulogy, Fifth edition, Mosby 1998 referenced below and Encyclopedia of Immunology (1998), Abbas et al. Cellular and Molecular Immunology 2000, Harcourt & Brace, the contents of which are incorporated by reference herein). Antibodies for many such ligands are known or could be readily made by eg. phage display (see references herein including *J Immunol Methods* 1999 Dec 10;231(1-2):65-81), and natural ligands for such markers or functional analogues thereof are in some cases known or could be made by recombinant DNA technologies referenced herein (see also Cellular & Molecular Immunology 4th Edition, Abbas Ak et al. WB Saunders and Company 2000, Antibody Fusion Proteins, Stevan M Chamow , Avi Ashkenazi Eds. ISBN 047118358X May 1999 Wiley; Kontermann, R., et al.(Eds.) Antibody Engineering, Springer 2001. ISBN 3-540-41354-5; Antibody Engineering:A Practical Approach David J. Borrebaeck Oxford University Press, 1995; Antibody Engineering; Antibody Chiswell, Hennie R. Hoogenboom, John McCafferty Oxford University Press,1996; Antibody Engineering Protocols, Sudhir Paul (1995) Humana Press; Antibody Expression & Engineering (1998) Henry Y. Wang, Tadayuki Imanaka, American Chemical Society). The term modulation is used broadly to refer to any change, directly or indirectly, in an immune function or effect, as broadly understood. Many such forms of modulation are well known in the art (some are exemplified herein), and therefore these need not be specifically recited (for a review of such effects see for example Roitt I et al. Immulogy, Fifth Edition, Mosby 1998; Encyclopedia of Immunology ; (1998) Morgan Kaufmann Publishers, ISBN:0122267656).

6. In one aspect the invention contemplates that the multifunctional ligand exerts its function substantially (ie. upon gaining entry into lymphatic system and when bound to the lymphatic endothelial cells, which is dependant on the mode of administration) within the lymphatic system, *on cells and/or molecules circulating through the lymphatic system*, for example with respect to some embodiments, for greatest effect, to avoid an undesired degree of immunosuppression (for example, embodiments where immune cells are targeted for ablation and/or apoptosis). Preferably, such effect, is exerted at least in part, and preferably substantially to the exclusion of regions within lymphatic system that house at the time of administration non-circulating cells (eg. thymus, bone marrow, and various parts of the secondary lymphoid tissues) or/and with respect to some embodiments (excluding for example those related to immunization or mopping up toxins or antibodies) preferably, non-activated cells. This specificity of targeting can be accomplished in part to the natural

distribution of the lymphatic endothelium associated marker of choice, the mode of administration and various targeting strategies herein described.

7. For example, the invention contemplates modes of delivery that to *varying degrees* ensure a greater degree of lymphatic system targeting, for example administration directly within the lymphatics, adminstration in tissues that drain to the lymphatics or parts thereof, intravenous delivery, as are well known to those skilled in the art, preferably in each individual case at strategic sites of administration that are most pertinent or selective for the disease in question, to the extent that selectivity is desired. The invention contemplates a variety of different size multifunctional ligands (MRU, single domain, scFv, Fab, minibodies, F(ab)2, F(ab')2, substantially whole antibodies etc. and known or obvious multimers thereof referenced herein and in the referenced literature) that are most suitable (eg. for small enough or, for example, having longest half life in circulation) for particlar modes of administration to the extent that this is a limitation (eg. size, where drainage into the lymphatic system is sought to be increased or optimized).

8. In a preferred embodiment the invention contemplates that the immune function exerting moiety of the multifunctional ligand comprises (eg. by way of recombinant fusion, conjugation etc.), or binds to (such antibodies are known or may be made by phage, ribosome or other such 'display' methods), so as to present the functional part of an adhesion molecule (molecule involved in cellular adhesion), for example an endothelial adhesion molecule such as a selectins, ICAMs (eg. ICAM-1, ICAM-2) V-CAM, MAdCAM-1 or functional analogues or portions thereof (see for example USP6143298, 5512660, 5861151, 5489533, 5,538,725, 6037454, 5565550, *Circulation* 2001 Feb 27; 103(8):1128-1134, and specific examples/references recited below) in order to control cell traffic including facilitating cell anchoring within the lymphatic system, including for example to facilitate interaction with another "arm" (functional moiety) of the multifunctional ligand or a second etc. multifunctional ligand or an immune cell (or a cell-sized latex sphere as described herein - for this pupose the adhesion molecule may be on the surface of another, preferably multifunctional-ligand-anchored latex sphere or on a similarly anchored cell) as well as combination therapies, for example, with therapeutic entities that enhance or inhibit leucocyte adhesion, or multifunctional ligands or antibodies that bind to one of their corresponding ligands on immune cells (eg. intergrins) or other ligands eg. CD44, to facilitate control and/or some selectivity of cell entry into the lymphatic system, for example, for reactivity with the multifunctional ligands of the invention.

9. The invention also contemplates that one or more multifunctional ligands in which the immune function exerting moiety comprises an antibody type molecule targeted to a particular cell surface ligand may be able to mimic effect of such adhesion molecules, as discussed below (any such discussion of an antibody mimicking this function is unless otherwise stated not intended to limit the broader concept of utilizing any class of molecule that would facilitate anchoring or controlling, eg. slowing the passage of cells through the lymphatic vessels). It is to be understood that there may be limitations in the number of cells that can be targeted for ablation in the lymphatic system by slowing the passage of cells, particularly for the purpose herein specified of allowing them the requisite period of residence within the lymphatic system for immune cell targeting or interaction or prolonged interaction with multifunctional ligands of the invention for binding purposes while bound to the lymphatic system endothelium, for example, certain end stage lymphomas/leukemias. In this particular context it is to be understood that: 1) the invention may have greatest application when the multifunctional ligand is administered so as to primarily target cells within the circulatory system, or as an adjunct therapy, or for remission or near remission conditions, or when combined with hyaluronic acid therapy. For example, the invention contemplates that an effective amount of hyaluronic acid is pre-administered to tissues draining to the lymphatic system so as to initially occupy binding sites on LYVE-1 primarily in the smallest lymphatic vessels and thereby minimize excessive binding within the narrowest vessels.

10. In a preferred embodiment said first portion binds to LYVE-1 described below.

11. In a preferred embodiment, said first portion is fused, conjugated or otherwise linked directly or indirectly to an immunizing moiety, for example an antigen, epitope, mimotope or peptide etc. presenting/incorporating entity/scaffold that generates by itself or with the help of one or more cytokines, costimulatory molecules and/or adjuvants etc. an immune response to a desired antigenic determinant (this term is used broadly to correspond at least in scope to the overlapping groupings: antigen, epitope, mimotope or peptide), for example an anti-idiotypic antibody, an antibody component which is capable of binding to a T cell activating entity for example a cell (eg. an APC see *Int Immunol* 2000 Jan; 12(1):57-66 or other cell having eg. immune modulating activity eg. see USP 6,004,811) which is for example genetically engineered to express relevant ligands for activating (or with respect to functions not necessarily related to immunizing, anergizing, tolerizing or otherwise modulating the activity of), an immune cell for example a B cell or T-cell, for example an MHC-peptide and B7 co-stimulatory molecules for activation of T-cells (see for example *Proc Natl Acad Sci U S A* 2001 Jan 2; 98(1):241-246 see also Tham EL et al. J of Immunological Methods Vol. 249(1-2)(2001) p111-119 with respect to latex spheres that can be used for this purpose), or for example a CTLA-4 scaffold, a peptide fused to an Fc domain (see WO 01/18203) a HSP-peptide

complex/conjugate, an MHC protein or peptide complex etc. It is also contemplated that the absence of costimulatory molecules for presentation in a co-stimulatory fashion with an MHC peptide complex will cause a tolerizing effect. Accordingly the invention is also directed to a multifunctional ligand comprising an immune function exerting moiety which comprises an MHC, preferably complexed or otherwise linked to a peptide. Peptide linking may for example be effected independently, naturally or for example through causing release of peptides from an MHC peptide or HSP peptide complex by injecting a weak acidic solution into tumor eg. just prior to excision. Suitable such solutions which may for example be combined with a cytokine , eg.IL-12 and/or adjuvant are known in the art.

12. In a preferred embodiment said immune function exerting moiety comprises an anti-idiotypic antibody, for example an antibody that a) mimics, for example, a cell surface expressed tumor associated epitope, a virus or other infectious agent associated surface epitope, a toxin, an immune stimulatory, costimulatory, inhibitory, or otherwise interactive ligand; or b) serves to bind to the idiotype (ie. paratope) bearing antibody to which it binds as an anti-idiotype, for example an autoimmune antibody, etc. or an antibody bearing a toxic moiety for removing such antibody from passage into the circulation.

13. In a preferred embodiment, the invention contemplates that the first multifunctional ligand is used for development, therapeutic evaluation or combination therapy in conjunction with a second different multifunctional ligand of the invention, to achieve a cooperative effect (for example, in the same composition or substantially contemporaneously administered (ie. to reach the same or an interrelated destination in a cooperative time frame) or in necessary or desired sequence/interval, etc.). An example of such cooperative effect is an interaction (not necessarily simultaneously) with two different immune cell surface ligands (for example via an antibody binding interaction), or to deliver different payloads eg. toxins, to a diseased cell see (USP 6,077,499). The invention also contemplates a method of effecting substantially coordinated interactions of differing temporal and spatial complexities, ranging from a somewhat proximal and contemporaneous delivery (eg. in the same composition) of a first multifunctional ligand having, for example, a cancer cell binding second portion, and a second multifunctional ligand having, for example, a cytokine binding Ab, eg. to reduce any toxic effects associated with toxic levels of cytokine release, a cytokine component (for example to harness the effect of such component as a means to attract one or more immune cells to kill a diseased cell or to harness the inhibitory effect of such component (eg. using one or more cytokines employed by cancer cells to evade immune cell targeting) eg. on undesired immune cell elimination or immune cell elimination of the multifunctional ligand, or a T-cell binding component (eg. anti-CD3) to harness the effects of such component on cancer cell killing optionally with a concomitant object of assessing possible counterproductive immune cell elimination (eg. as would be enabled by using a radiolabelled multifunctional ligand and determining the disposistion of the label over time) of the multifunctional ligand.

14. Also contemplated are methods to implement more spatially and/or temporally sensitive interactions. For example, when administered in empirically determined suitable proportions and in empirically determined sufficient total amounts for, at least, partial and/or local lymphatic-vessel-associated-ligand saturation or partial saturation to achieve proximal binding of a first to second multifunctional ligand (having regard to the route of administration eg. local saturation can be more readily accomplished by administration into the lumen of the lymphatic vessel). Two different such multifunctional ligands may be used, for example, to deliver two different immune function exerting moieties in substantial proximity to one another for contemporaneous interaction with two different ligands on an immune cell (ie. when it approaches the luminal wall of a lymphatic vessel). For example, this approach may be used to implement one or more effects including increased avidity to the cell for prolonged cell anchoring, which may positively impact on desired (in some embodiments) transfer of the multifunctional ligand from the lymphatic vessel wall to the target cell eg. for achieving an inhibitory effect via ligand binding (eg. assessed via duration of multifunctional ligand binding eg. quantitative or radioimage approximated label elimination)(N.B. this effect may be assessed with multiple copies of the same multifunctional ligand), delivery of a cooperative payload eg. different entities which contribute to the same or a different mechanism of cell killing, counterparts in a two componient interaction (biotin-avidin), which preferably yields evidence (preferably quantifiable evidence) of the interaction, for example an enzyme-substrate interaction to quantitatively assay the amount of an enzyme converted substrate (eg. using a conjugated prodrug and pro-drug conversion akin to ADEPT and assessing the extent of prodrug conversion eg by labeled anti-drug specific antibody). For example, the invention contemplates the use of a respectively linked catalytic antibody component (see for example US5658753:Catalytic antibody components) and labeled substrate or RNAase and labeled RNA etc.for this purpose. Another example, discussed in more detail below is the use of one multifunctional ligand for targeting (selectivity) purposes and another for implementing directly or indirectly a desired therapeutic effect, both ligands optionally being required to to give rise to a substantial probability of binding (the invention also contemplates that this strategy could be used with a single multifunctional ligand having two intra-luminally directed binding moieties).

15. The invention contemplates that such interactive entities may be conjugated fused or otherwise linked to a respective first and second multifunctional ligand for achieving a cooperative interaction between adjacently bound such ligands.

16. The invention contemplates that adjacently interacting multifunctional ligands yielding detectable evidence of the interaction, could be use in a method to assess eg. a) luminal ligand saturation for dosing, b) multiple simultaneous binding interactions, and c) perhaps most spatially sensitive, development of a process to achieve cross-linked binding with multiple eg. immune cell ligands eg. a costimulatory immune effect (ie. the effect of different simultaneous interactions eg. on stimulation, inhibition etc.of eg. an immune cell for example combining a first multifunctional ligand capable of selectively binding to, conjugated to or fused to a B7component (see *J Immunother* 2001 Jan-Feb; 24(1):27-36; *J Immunol* 2001 Feb 15; 166(4):2505-2513; Chalitta PM et al. J. Immunol. 160:3419-3426) and a second multifunctional ligand capable of selectively binding to, conjugated to or fused to an MHC molecule delivered initially with or without peptide. For example, the invention contemplates using various amounts/proportions of multifunctional ligands having antibody components fused or conjugated to or capable of binding selectively to, for example an MHC class I or II peptide complex and recombinant B7-1-Fc and/or B7-2-Fc respectively (see Eur J Immunol 2001 Jan; 31(1):32-38; *Eur J Immunol* 2001 Feb; 31(2):440-449) (for tumor reactive peptides see for example *J Immunother* 2001 Jan-Feb; 24(1):1-9). In this latter connection (cross-linking type interaction), and/orfor permanence of binding or ease of attaching other cooperative entities (for example biotin coated or conjugated radionuclides, liposomes or other payload carrying entities (eg. see for example US patents 5439686, 6007845, 5879712, 5456917, 6165502, 5079005, 5888500, 5861159, 6193970, 6190692, WO 00/69413, WO 01/07084) the invention contemplates biotinylating the two multifunctional ligands and linking the two biotinylated cooperative mulfunctional ligands with avidin, streptavidin (or other modified forms thereof eg. deglycosysylated avidin or using other complementary linking components- see eg. US Patent (USP) 6,077, 499).

17. The invention also contemplates enhancing the cross-linking of the multifunctional ligands of the invention through complementary components such as biotin and avidin.

18. Preferably, with respect to, for example, increasing selectivity of targeting certain cells (eg. to induce immune tolerance), the invention also contemplates that a first multifunctional ligand is used to bind to a marker specific to a particular kind of cell (eg. activated immune cells) and a second multifunctional ligand (which may not be specific for activated immune cells) is used to modulate the activity of the immune cell (for example inactivate it or reduce its disease causing capability directly or indirectly by binding to it). For example, where the marker is used to determine the selectivity of the targeting but cannot be used for modulating its activity, it is contemplated that the functional affinity of one or both the first portion and second portions of one or both of the cooperating multifunctional ligands can be selected to at least partially control the selective modulating effect of the pair, for example both interactions would be required for the second multifunctional ligand to have an optimal opportunity to bind. For example, the functional affinity for the target cell is relatively weak for the purpose of attaching to the eg. immune cell for a sufficient duration (eg. so as to yield the effect of becoming attached to the immune cell in preference to the lymphatic vessel), compared with that of the first multifunctional ligand (ie the one that accomplishes the selective recognition through binding) to *reduce the likelihood* that the second moiety will bind in the absence of binding of the first moiety (notably a similar type of coordinated interaction ie. two binding interactions, is naturally used for cell adhesion). (NB. this type of coordination has application ie. both specificities are optimally required for binding, to a single multifunctional ligand, having a divalent immune function exerting moiety eg a triabody or tetrabody or for cross-linking and other types of coordinated interactions). In a preferred embodiment, if transfer of binding of the first multifunctional ligand to the immune cell is not desired its functional affinity of the first portion to the lymph vessel can be greater than that of its second portion, while the reverse could be true for the second multifunctional ligand. It will also be appreciated that antibodies which cross-link for example an integrin and a marker of immune cell activation could be used to limit the number of activated immune cells that migrate through the lymphatic system. For example bispecific d Abs, diabodies, etc. in which the functional affinity of each specific binding portion individually does not srongly favour binding, could be used to selectively target specific sub-populations of immune cells or even specifically activated immune cells (for example antibodies that recognize particular antigen / peptide specific T cell or B cells).

19. Accordingly, more generally speaking, the invention is directed a bispecific ligand, preferably a bispecific antibody, having a first portion which binds to a ligand which differentiates between members of the same immune cell population (eg a particular type of T cell) and a second portion which binds to a second ligand on the same cell, which binding exerts directly or indirectly a desired effect, wherein the functional affinity of said first and second portions are selected so as to substantially increase amount of immune cells in which both such portions are bound to their respective ligands relative to those which a single such portion is bound to a single ligand and preferably wherein the amount of immune cells to which the bispecific ligand is not bound is

substantially greater than the number of immune cells that are not bound when compared to using a bispecific ligand having the same specificity and for example a 10^1 to 10^7 (preferably 10^1 to 10^6, preferably 10^3 to 10^6, preferably 10^3 to 10^5) increase in affinity of one or both portions. This invention also contemplates that binding to the ligand which differentiates between members of the same population (a particular type of T cell) does not have a negative consequence other than to cause the molecule to be ineffectual unless both of its portions are bound and that its binding is itself sufficient for binding and/or stronger relative to the second portion by two fold to 5 orders of magnitude ,preferably 1 to 3 orders of magnitude. The term substantially greater imports medical significance and may preferably be 15% - 10000% greater. The foregoing examples are not meant to be limitative.

20. In a preferred embodiment, the invention more broadly speaking contemplates a two ligand interaction (using one or more multifunctional ligands) wherein for example both are required or increase the likelihood of interaction and wherein the interaction of at least one contributes to specificity, though not necessarily to modulation, thus permitting a broader selection of modulators including those that but for the selectivity enhancing effect of the cooperating ligand and the lymphatic system venue, would be toxic in the desired therapeutic dose. Examples of markers that could assist in selectivity include those are unique to, for example, activated B cells or T cells or those having particular specificites in virtue of unique Ig type receptors. Examples of ligands on, for example immune cells, through which modulation/inhibition/stimulation etc. (including, for example apoptosis), for example by antibody binding or supply of a natural interactive ligand, are well known. Some examples are provided herein. Combinations and permutations of markers and ligands for selectivity and exerting an immune effect such as modulation/inhibition/stimulation referred to herein or in the literature incorporated herein by reference or well known in the art are contemplated to be within the scope of the invention.

21. It will be appreciated that a combination of factors, such as dose, using additional molecules that increase or decrease migration or adhesion optionally in a tissue targeted manner, route of administration (eg within tissue that best drain to lymphatic vesssels or a portion thereof), use of cytokines, etc. and immune modulating drugs, as well combination therapies with known entities, can be employed in various combinations for strategies of harnessing the unique properties of the multifunctional ligand of the invention, to achieve a selectivity enhancing and/or modulatory/inhibitory/stimulatory etc or otherwise cooperating effects with respect to the desired target population of cells. Unless their function are self-evidently conflicting the invention contemplates all permutations of the multifunctional ligands disclosed herein or in the literature incorporated by reference hererin as well as those evident to persons skilled in the art whose mention is omited.

22. In a preferred embodiment, the immune function exerting moiety binds with greater functional affinity to its target ligand than said first portion binds to its target ligand. For example said immune function exerting moiety may bind with greater avidity (preferably at least 2 times greater (divalent vs. monovalent) and lesser or greater affinity (eg. within a range of $1x10^{-6}$ to $1x10^6$ fold) or with the same avidity and greater affinity (eg. up to$1x10^6$ fold). In applicable aspects, the invention contemplates that this increased functional affinity can be employed to effect transfer of a lymphatic vessel bound multifunctional ligand (eg. a bispecific antibody) to a cell passing through lymphatic system. The invention also contemplates a method comprising radiolabelling the mutifunctional ligand to assess, for example, the degree to which immune cells at a disease site have passed through the lymphatic system. Certain aspects of the invention, discussed herein, relate to a multifunctional ligand based system of targeting a particular immune cell ligand for stimulation, inhibition etc. predominantly within select portions of the lymphatic system that contain migrating cells (although some general targeting can controllably occur before the multifunctional ligand binds to the lymphatic system or when the multifunctional ligand releases from the lymphatic system without having found its target within the lymphatic system) will have at least a partially selective effect on targeting disease causing/mediating immune cells (eg. activated with a specificity that causes the disease) as opposed to non-disease causing/mediating cells, in the case where such ligand is also expressed on such other immune cells eg. of the same type eg. T cells. This permits targeting of immune cells primarily within the portions of the lymphatic system that contain migrating cells particularly disease causing/mediating cells while minimizing immune system dysfunction. This effect can be even more selectively accomplished, for example, by delivering the multifunctional ligand directly into the lymphatic system and within a time frame which is shorter that the normal duration of binding of the multifunctional ligand determining the degree to which the multifunctional ligand is bound to such diseased related cells at the disease site and similarly the degree to which it is bound to the cells unrelated to the same disease eg. via radiolabel. As discussed more fully below, the invention also contemplates a multifunctional ligand based system of assessing the effects of certain types of immune stimulation eg. how stimulating enhanced migration or adhesion, will differentially affect disease activated cell migration through the lymphatic system to enhance such disease cell targeting within the lymphatic system. For example, for tumor cell targeting and stimulation of disease-activated immune cells the invention contemplates evaluating cytokine (eg. TNFα) linked anti-angiogenic marker antibodies, optionally, preferably in combination with anti-tumor vaccination strategies, to direct disease activated immune cells to tumor site and the lymphatic system for

further immune stimulation. Based on a "bait and trap" type approach, ligands such as OX40L and CD44 may also be assessed for this purpose.

23. In this connection and more generally the invention also contemplates using a bi-specific antibody, for example having a lymphatic endothelial binding first portion and for example a cytokine binding second portion, wherein the cytokine binding portion has a lower functional affinity for the cytokine (for example 1 x 10 −6 to 0.9 fold) compared with that of its natural receptor on an immune cell. It is contemplated that a multifunctional ligand of the invention could be used optionally in conjunction with a multifunctional ligand which displays a functional adhesion molecule (a selectin, ICAM, etc.) to assess the optimal parameters for transfer of the cytokine, for example, as is known to occur by monitoring the effects of cytokine release attributable to such cytokine transfer. It will be appreciated that this information or approach could be used to optimize the binding parameters for other ligands as well (eg. anti CD3) and could be employed not only in lymphatic system but to locally deliver inhibitory or stimulatory cytokines or other ligands to certain tissue targets, for example new blood vessels forming within tumors or other tissue specific markers.

24. The foregoing strategies could be used as part of a primary, adjunct or low disease burden therapy.

25. In a preferred embodiment, the second portion comprises a ligand which is capable of binding to an immune cell for example B cells, T cells etc, preferably in one embodiment to assist in cell killing or immune modulation of a target cell (re NK cells see for example US 5770387)(see also US6071517:Bispecific heteroantibodies with dual effector functions; Bispecific antibody-mediated destruction of Hodgkin's lymphoma cells. *J Immunol Methods* 2001 Feb 1; 248(1-2):113-123; Bispecific antibody-targeted phagocytosis of HER-2/neu expressing tumor cells by myeloid cells activated in vivo.J Immunol Methods. 2001 Feb 1; 248(1-2):167-182 as well as *J Immunol Methods* 2001 Feb 1; 248(1-2):103-111).

26. With respect to avidity, affinity and other elements of design including size, blood clearance, additional functionality etc.the multifunctional ligand may be, for example, a bispecific antibody having a monovalent first portion and a monovalent second portion, a bispecific antibody having a divalent first portion and a divalent second portion, a trivalent trispecific antibody having a monovalent first portion and a second portion comprising a monovalent immune function exerting moiety which binds, for example, to a target ligand on a target diseased, disease causing or immune cell, and for example, a monovalent portion which binds to an immune cell which assists in killing or modulation for example anti-CD3 or anti-CD28 antibody component, a tetravalent trispecific antibody having a monovalent first portion and a second portion comprising a divalent immune function exerting moiety which binds, for example, to a target ligand on a target diseased, disease causing or immune cell, and for example, a monovalent anti-CD3 or anti-CD28 antibody component (it is contemplated that this orientation might advantageously position the anti-CD3 component for interaction with a T-cell almost exclusively when the first portion is not bound to the luminal wall of a lymphatic vessel), a trivalent bispecific antibody having a monovalent first portion and a second portion comprising a divalent immune function exerting moiety, for example, one which binds, for example, to a target ligand on a target diseased, disease causing or immune cell. The antibody subunit may be for example, a Fab, a substantially intact antibody, a single domain antibody (see also Hufton SE. Dis Markers 2000;16(1,2):37 Single domain human immunoglobulin fold-based biomolecules; Antigen specificity and high affinity binding provided by one single loop of a camel single-domain antibody. J Biol Chem. 2001 Jul 13;276(28):26285-90. Optimal Design Features of Camelized Human Single-domain Antibody Libraries. J Biol Chem. 2001 Jul 6;276(27):24774-24780; Recognition of antigens by single-domain antibody fragments: the superfluous luxury of paired domains.Trends Biochem Sci. 2001 Apr;26(4):230-5; Llama heavy-chain V regions consist of at least four distinct subfamilies revealing novel sequence features. Mol Immunol. 2000 Aug;37(10):579-90) a minibody an scFv or a minimal recognition unit (MRU eg see US6174691:Minimum recognition unit of a PEM mucin tandem repeat specific monoclonal antibody).

27. In a preferred embodiment, the multifunctional ligand binds to an immune cell which is associated with an autoimmune reaction, for example a CCR5-expressing cell. (see also Apoptosis genes and autoimmunity. Curr Opin Immunol. 2000 Dec; 12(6):719-24. for application herein)

28. In a preferred embodiment, the second portion comprises a cytokine component.

29. In a preferred embodiment, the second portion comprises a cytotoxic component.

30. In a preferred embodiment, the second portion of the multifunctional ligand comprises an internalizing antibody and a cytotoxic component.

31. In a preferred embodiment, the second portion consists of an antibody which binds to T cells, for example, an anti-CD3 antibody or an anti-CD28 antibody.

32. In a preferred embodiment, the second portion consists of a cytokine component.

33. In a preferred embodiment, the second portion comprises an antibody which binds to a target diseased, disease causing or immune cell and further comprises one or more components selected from the group consisting of a cytokine component, a cytotoxic component and an anti-CD3/CD28 component.

34. In another aspect the invention is directed to a composition comprising a multifunctional ligand and a pharmaceutically acceptable excipient.

35. In another aspect the invention is directed to a composition comprising a plurality of different multifunctional ligands.

36. In another aspect the invention is directed to methods and compositions for developing and evaluating the therapeutic value of stimulators, mediators, inhibitors etc. of immune cell signaling (eg. stimulatory, inhibitory, costimulatory), adhesion, migration,etc. including the effects of ligand/receptor blocking and supply of specific cooperative ligands, using the multifunctional ligands of the invention.

37. In a preferred aspect, the multifunctional ligands of the invention may be used to assess the effects of such compositions on the sub-populaton of cells that migrates into lymphatic vessels. In particular, the invention is directed to assessing the expectation that some disease causing, mediating or otherwise disease active immune cells have an enhanced ability/opportunity (and/or can be enhanced in their ability/opportunity to make their way into the lymphatic system) so that targeting of relevant ligands on that sub-population of cells within the lymphatic system will cause at least a partial selective targeting effect, preferably with positive effect on the dosing capability and choice of ligands ie. in terms of limiting more universal and/or deleterious consequences. The invention is also directed to a method of reducing the toxic side effects of a pharmaceutical composition comprising a multifunctional ligand in which the immune function exerting moiety is targeted to a ligand that is not found exclusively on disease causing, mediating or otherwise disease active immune cells, by administering said composition in a manner in which it enter more directly into the lumen of a lymphatic vessel. (It contemplated that immunization within the lymphatic system can also be enhanced in virtue of such selective targeting.) In particular, the invention is directed to a multifunctional ligand, a pharmaceutically acceptable composition therof and method of using same for assessing enhanced migration or enhancing migration of disease-active immune cells, said multifunctional ligand comprising an immune function effecting moiety which has an immune effect on an immune cell surface ligand ie. effects including signaling (eg. stimulatory, inhibitory, costimulatory, antagonistic, agonistic), including for adhesion and migration effects,etc. This may be accomplised practically, for example through ligand/receptor blocking eg. via antibody, or by antibody fusions/conjugates etc. that supply the natural ligand or a functional fragment or chemical/biological mimotope thereof. In a preferred embodiment the invention is directed to a multifunctional ligand in which the immune function exerting moiety is an antibody that binds to a ligand selected, for example from the group consisting of CTLA-4, IL-2 receptor, CCR5, CD44, CD134, CD3, CD28, CD2.

38. In another aspect the invention is directed to a composition comprising a plurality of different multifunctional ligands which exert a potentially cooperative immune effect with respect to an immune cell, for example binding to two or more different ligands on an immune cell, wherein said ligands are selected, for example from the group consisting of CTLA-4, IL-2 receptor, CCR5, CD44, CD134, from any of the ligands herein mentioned or referenced or preferably CD3, CD28, CD2.

39. The invention is also directed to a method of preventing metastasis during the course of surgical removal of a tumor comprising administering to a patient prior to surgical treatment of the tumor site, a pharmacetical composition comprising a multifunctional ligand in which the immune function effecting moiety binds to a tumor associated epitope on a cancer cell.

40. In another aspect the invention is directed to an immunocytokine having an anti-idiotypic antibody component which recognizes the paratope of an antibody which binds to a lymphatic vessel associated ligand and a cytokine component fused therewith or conjugated thereto. For example the cytokine component comprises IL-2 or a functional fragment thereof and/or IL-12 or a functional fragment thereof. In addition to their individual use in fusion proteins for tumor cell killing, combinations of Il-2 and IL-12 have been used successfully for this purpose. It is contemplated that such cytokine fusion could be used to target T-cells or phagocytic cells to a multifunctional ligand that has bound to its disease causing or diseased cell target, preferably having left the lymphatic vessel endothelium in preference for binding its target. In this connection it is contemplated that the functional affinity of the anti-idiotypic Ab for the first portion would be less than that of the first portion to the lymphatic endothelium, so as to minimize competition between the two. It is also contemplated that the delivery of the immunocytokine occur substantially contemporaneously but

separately and after that of the multifunctional ligand, optionally by a different route of administration.

41. Similarly the invention contemplates for the same purpose, a bispecific antibody having an anti-idiotypic antibody component which recognizes the paratope of an antibody which binds specifically to a lymphatic vessel associated ligand (preferably with lower affinity than that of the Ab for its target) and for example an immune cell binding portion eg. an anti-CD3 antibody or an anti-CD28 antibody component.

42. Thus the invention is directed to a method of targeting a diseased or disease causing cell for destruction by the immune system comprising administering separately but substantially contemporaneously to a subject hosting the diseased or disease causing cell, preferably in sequence with an interposed interval and/or by different routes of administration, first a multifunctional ligand in which the immune function effecting moiety binds to a diseased or disease causing cell surface associated epitope, and an immunocytokine or bispecific antibody as decribed in the immediately preceding two paragraphs.

43. In a preferred embodiment the invention contemplates modification of the multi-functional ligand to substitute one or more amino acids which reduce without functional impact on the molecule the number of immunogenic MHC II class peptide sequences within the molecule. This can be accomplished through procedures available to those skilled in the art, for example through the DeImmunisation services of Biovation Limited (see also US 5821123 and related Xoma patents).

44. Inasmuch as the invention is predicated on intraluminal lymphatic system targeting such lymph associaton may be alternatively implemented, in suitable circumstances by the method of delivering the multifunctional ligand, for example into the lumen of a lymphatic system vessel or (where the multifunctional ligand is not of an unsuitable size (see for example Ikomi, F. et al. Lymphology 32 (1999) 90-122, within a portion of body that drains to the lymphatic system (ie a portion of the lymphatic system), for eventual migration to the lymphatic system. Particularly, with respect to embodiments of the invention in which the immune function exerting moiety is targeted with greater functional affinity to a therapeutic target (ie. not the lymphatic system target), such lymphatic system oriented modes of delivery coupled with preferred targeting to the therapeutic target may combine, absent saturated binding to the therapeutic target, to better accomplish functional lymphatic targeting. Accordingly, in a broader aspect the invention is directed a lymphatic system targeted multifunctional ligand in which the second portion is as described herein and in which the specificity of the first portion exclusively for a lymphatic system is inessential. In this connection, the invention contemplates targeting markers on lymphatic vessels that are also present; for example on blood vessel endothelial cells (eg. VEGF2). (with respect to lymph specific markers see also Birner P. et al. Clin Cancer Res 2001 Jan; 7(1):93-7 "Selective immunohistochemical staining of blood and lymphatic vessels reveals independent prognostic influence of blood and lymphatic vessel invasion in early-stage cervical cancer" and published references to the markers therein mentioned.)

45. In the case of purely sustained release aspects of the invention where the first portion is temporarily anchoring a second portion for eventual release back into the circulation, the use of term immune function affecting moiety with reference to the role of the second portion does not adequately accommodate the breadth of the invention since any form of disease palliating active moiety or entity which exerts its effect elsewhere than at the lymphatic endothelial cell may gain advantage from this form of delayed delivery (depot effect) or anchoring.

46. Furthermore, in another preferred aspect, the second portion is capable of binding directly or indirectly (eg. binding to an entity which in turn binds to a target entity) to a target entity, for example a therapeutic entity (for example to mop up excess such entity that does not immediately reach its target (eg. an entity that is toxic elsewhere in the body), a toxic entity including an entity which is not per se toxic but the presence of which is undesirable at a particular time or in particular amount or concentration (eg. a cytokine, for example when released as a result of anti-CD3 therapy), to *redirect* an an entity to a target, for example a therapeutic entity, for example through the instrumentality of an antibody portion that is directed to that target (eg. a multifunctional ligand in which the second portion comprises an anti-tumor antibody portion that is conjugated to streptavidin, to retarget biotin conjugated radionuclide back to the tumor (see Martin J. et al. (1997) Cancer Chemother, Pharmacol. 40:189-201), to temporarily anchor liposomes or other carriers of entities (eg. drugs) having an direct or indirect beneficial effect elsewhere.

Detailed Description of Preferred Embodiments

In a preferred embodiment, the invention provides a multifunctional ligand having, at least, a first portion which binds to a lymphatic vessel associated antigen/receptor (and thereby exerts, not necessarily to the exclusion of other effects) at least an anchoring function, and a second portion having at least one independent immune

function. The term "immune function" is broad in intent including but not limited to direct or indirect and primary or corollary effects related to simple targeting, tolerance, immunization, stimulation, inhibition, modulation or various other immune related effects (other than simply forming part of the entity which blocks the lymphatic endothelial associated ligand). The term independent is used to exclude only an effect specifically targeted towards the ligand (blocking) or cell bearing the ligand to which the first portion of the multifunctional ligand is bound, which is not contemplated as an object of the invention. The invention contemplates rather that the immune function is exerted, for example, vis-à-vis immune cells or molecules or against cancer or infected cells to affect an immune function that relates to assessment, diagnosis, therapeutic modeling, or treatment of various disease states such as autoimmune disease, transplant rejection, cancer and infectious disease. In a preferred embodiment, the invention contemplates that the independent immune function is exerted through a physical ligand-ligand interaction. In a preferred embodiment the multifunctional ligand has an ability to bind in the manner of an antibody in virtue of at least one of the first or second portions, and preferably at least the first portion. The lymphatic system directed first portion may in some embodiments (LYVE-1) be hyaluronic acid or analogues thereof that have the appropriate binding capacity. In a further preferred embodiment the second portion binds to a target ligand on a cell or molecule (eg. a cytokine or autoimmune antibody) which passes through the lymphatic system. In a more preferred embodiment the multifunctional ligand is a bispecifc antibody. The term antibody is used to refer to any antigen binding fragment of an antibody that substantially has the binding capability of an antibody including anti-idiotypic antibodies, and therefore the term bispecific antibody is used (unless the context implies a more specific usage) in a functional sense to refer to at least two different specificities (including trispecifc antibodies etc.) and includes well known entities which are diabodies, triabodies, tetrabodies, minibodies, scFv dimers, etc., and entities in which one or both binding moieties are scFv or single domain type antibody fragments or dimers etc of such fragments (with respect to single domain antibodies see for example Camel single-domain antibodies as modular building units in J Biol Chem. 2000 Oct 25, & Mulligan-Kehoe U.S. patents).

The term "anchoring function" is used broadly to refer to physical attachment for a period which renders the second portion of the multi-functional ligand capable of exerting its immune function. For example where the function of the second portion is to interact with a cell passing through the lymphatic vessels, for at least a period which permits sufficient interaction for the desired effect.

The term ligand is used very broadly herein to refer to any moiety, preferably in some cases, a specifically interacting moiety including binding moieties (eg antibodies, receptors etc.) and bound moieties (eg antigens, epitopes etc) and/including otherwise interacting moieties (eg. chemotactic interactions or interactions that require multiple points of interface eg. cross-linking or multi-component epitopes). In other words, the term ligand is used broadly to refer to any entity or part thereof which can be subject to an intermolecular interaction that can result in binding. The term moiety is used broadly and non-limitatively to refer primarily to a functional part of an entity, and may refer to even the whole of the entity depending on the context in light of the broadest concept of the invention.

Optionally, depending on the mode of delivery and the relative functional affinity of the respective first and second portions, the multi-functional ligands of the present invention, may exert their immune function primarily in lymphatic system and also significantly before and optionally after entry into the lymphatic system. In a preferred embodiment the multifunctional ligand is capable of simulating a depot effect by binding for a prolonged period to the intra-luminal lymphatic endothelium for later release over time back into the circulation. The choice (avidity effect resulting from multiple binding "arms") and affinity of the binding molecule as well as various, preferably controllable factors impacting on any "undulating" movements of the lymphaticvessels (eg. water consumption)or competitive binding is contemplated to impact the binding time.

With respect to the depot and delivery aspects of the invention discussed herein, it is contemplated the second portion of the multi-functional ligand of the invention may have at least primary medicinal effects that are not immune function related as broadly understood.

It is to be understood that a use of a slash (/) means the broader of "or" or "and/or" unless to the context dictates otherwise.

Some immune interactions require, prefer or are capable of being enhanced via coordinated ligand interactions, for example for optimal immune stimulation, for example, specific costimulatory ligand interactions eg. CD80/CD86 interactions with CD28, or for example, interactions aimed at tolerizing or otherwise inhibiting or reducing immune effects or preventing such inhibition (for example using anti-CTLA-4/CD152 see related U.S. patents, for example 6,051,227, 5,844,095) (see also Hodge JW et al. Ernst Schering Res Found Workshop 2000 (30):23-52 and Immunological Reviews Vol 172 Dec 1999, Entire Issue).

The invention contemplates modeling, evaluating and/or effecting these interactions for therapeutic intervention within the lymphatic system through the substantially contemporaneous use of different multifunctional ligands of the invention. Furthermore, control of the relative proportion of each of the different ligands permits different spatial interspersion of these ligands on the intraluminal suface of the lymphatic system (primarily) so as to provide controlled variability of spatial configurations appropriate for optimizing the coordinate interaction with multiple ligands on another entity, for example immune cells or cancer cells. This strategy also permits controls on avidity that extend beyond the choice of valency for a given single multifunctional ligand for controlling the nature and duration of the coordinate interactions including the duration of temporary anchoring, for example to allow cancer

cells to be killed by immune cells, as well delivery of, for example, cytokines (through cytokine antibody fusions), superantigens etc. to the site of interaction. Such coordinate interactions may be substantially contemporaneous or sequential, for example the effect of a first interaction with a first multifunctional ligand slowing the progression of a cell or infectious agent through the lymphatic system for eventual reation with another first multifunctional ligand (ie of the same type) or reaction with a second type of multifunctional ligand. The invention also contemplates as a strategy, alone or in combination with other strategies: 1) delivery of a multifunctional ligand of the invention to a particular site of action for the purpose of exerting, for example a local effect, with the result of causing the multifunctional ligand (whether or not it has exerted its effect, provided that or to the extent that it remains functional in at least one aspect) to subsequently be targeted to the lymphatic system for exerting a second effect (be it the same or a different disease counteracting effect) including simply elimination, or return back to the circulation (ie. where the ligand is selected (eg. based on size, immunogenicity etc.) to be preferably minimally eliminated (at least not maximally eliminated) by the body in the course of its circulation, having regard to competing design considerations) for example, in the case of multifunctional ligand which is an anti-tumor ligand that has some residual binding to normal tissues, to set up, in effect, a site of competitive binding that advantageously impacts (ie.reduces) undesired binding more than desired target binding; 2) delivery of a multifunctional ligand of the invention or an entity that binds to a multifunctional ligand of the invention to a particular site of action eg. local disease mediating immune cells, for the purpose of simple binding with the expectation that a delayed immune or other effect will be exerted within the lymphatic system. Accordingly, the invention is also directed to a composition comprising at least one and optionally a plurality of different multi-functional ligands of the invention. The invention is also directed to such a composition when combined with a pharmaceutically acceptable carrier for example those that may be suitable for one or more of the various well known and heretofore used routes of administration including intravenous, intradermal etc which (for present purposes) are preferably not incompatible with delivering a multifunctional ligand of the invention to the lymphatic system. The invention is also directed to therapeutic compositions comprising a multifunctional ligand of the invention and to methods of treatment using such compositions. The invention is also directed to method of : 1) evaluating the therapeutic effect of a particular therapeutic entity against a particular target with reduced effect on undesired targets; 2) facilitating elimination a therapeutic entity; – by administering the therapeutic entity as part of or in circumstances which permit interaction with, a multifunctional ligand of the invention.

The invention also contemplates cannulating particular portions of the lymphatic system to localize the delivery of a multifunctional ligand (see United States Patent 4,911,690) , for example 1) to accommodate or further accommodate the treatment of conditions in which the immune affecting molecule has an undesirable systemic or localized side-effect if delivered otherwise; 2) for the localized delivery, as required, of larger molecules, complexes (eg. for temporarily anchoring MHC-peptide complexes) or otherwise associated (at least temporarily) entities (ie. associated other than through complex formation) etc. and/or 3) for the localized delivery of additional compositional elements eg. adjuvants, cytokines (see Immunological Reviews 2000 Vol 177 p. 5-246; Nature Immunology Feb 2001 Vol 2 No. 2 page 89), or for affecting only subsets of populations of cells or molecules that pass through the lymphatic system or a desired portion of the lymphatic system. The invention also contemplates methods of selective, enhanced or localized, targeting/ delivery by administering multifunctional ligands of the invention as well as methods (including methods directly or indirectly employing the multifunctional ligands of the invention) of *enhancing / inducing* entry of cells or molecules, particularly immune cells (ie. cells having an immune system function as broadly understood) or subsets thereof, to the lymphatic system or a portion of the lymphatic system, for example for the purpose of direct or indirect interaction with the multifunctional ligands of the invention (in order to be acted on directly or indirectly, by multifunctional ligands of the invention) or for recruiting cells that will for example kill or modulate the activity of other cells, for example kill cancer cells or infected cells that will have, are having or have had direct or indirect interaction with the multifunctional ligands of the invention, as discussed further below, for example in the case of cancer, by targeting immunocytokines to the disease affected tissue eg. using cytokines eg. TNFα fused to antibody that binds specifically to tumor cell markers or markers for angiogenesis. Similarly tissue targetted as opposed to disease targeted immunocytokines could be used selectively recruit immune cells within that tissue for example a diseased tissue to enter the lymphatic system for such purposes including for example interaction with a multifunctional ligand of the invention.

It is also contemplated that a single multifunctional ligand can have multiple requisite interactive functionalities for example to stimulate, attract, anergize (or otherwise inactivate) sub-populations of B-cells of T cells via the use, for example, of trivalent or tetravalent antibodies and antibody conjugates/fusions thereof having multiple ligand interactive capabilities (see also for example technologies being developed for selection of successful binders by phage or ribosome display (see for example WO 01/00866; *Adv Protein Chem* 2000; 55:367-403). A particular application of this technology for application to this invention are antibodies which retarget T-cells to tumor cells (see for example Manzke O. et al. Int. J. Cancer 82, 700-708 (1999); *Br J Cancer* 2000 Jan; 82(2):472-9; *J Control Release* 2000 Feb 14; 64(1-3):229-39 as well as related references, cited therein or citing these publications.

The present invention accommodates such technology through multispecific antibodies or alternatively obviates the need for combining a T-cell receptor type molecule with the primary immune function effecting moiety (eg. a cancer cell binding moiety) by using a separate multifunctional ligand which combines, for example, a first portion and a second portion comprising a T-cell interacting moiety (eg. anti-CD3). This is accomplished by administering in the same composition or substantially contemporaneously an amount of the second multifunctional ligand that provides, as may empirically predicted by assessing the dispersion of the marker on the endothelial cell, a strong probability (eg. .001-100%, optionally 1-100%, optionally 5-100%, optionally 10-100%, etc) that the T cell will be

targeted in the vicinity of a given lymphatic endothelial cell that happens be proximal to the cell sought be targeted eg the cancer cell. It is self-evident that a 50/50 proportion of the first and second multifunctional ligand will yield a strong chance that a second multifunctional ligand will be immediately adjacent on a particular given side (assuming for the sake of argument that there are sides when in reality the dispersion of the lymphatic endothelial marker is governing). It is also contemplated that adjacent multifunctional ligands may be linked for example through linkage effective pairs of ligands (avidin-biotin), the second portions having an antibody component which binds to a common ligand (eg on a liposome (see US 6197333 and refs. therein cited) or other pharmaceutically acceptable micro/nano particle/sphere of preferably selectable size for optimal spacer or endothelial cell protective purposes) and that such entities could optionally also be employed to house and deliver a payload to a given target vicinity.

In one aspect the multi-functional ligands of the present invention provide for a method and preferably a means for evaluating and/or inducing immune tolerance (with respect to B cells see strategies discussed in Immunological Reviews 2000 Vol. 176 pp. 5-247).

It is believed that immune tolerance is enhanced or prolonged through prolonged /strategic exposure to tolerance inducing and/or enhancing molecules for example prolonged antigen exposure (see Wang Y et al. Eur. J. Immunol. 2000; 30(18):2226-2234; Encyclopedia of Immunology ; (1998) Morgan Kaufmann Publishers, ISBN:0122267656; Hoyne GF *et al. Immunology* 2000 Jul; 100(3):281-8; Lerner CG et al. J Immunol. 2000 Apr. 15; 164(8): 3996-4002; Grossman Z. et al. *Semin Immunol* 2000 Jun; 12(3):197-203; discussion 257-344 Textbook of the Autoimmune Diseases by Lahita R. et al. ISBN: 0781715059 Lippincott Williams & Wilkins; Multi-Systemic Auto-Immune Diseases : An Integrated Approach Dermatological & Internal Aspects ISBN: 0444818960 Elsevier Science ; Arthritis and Allied Conditions - A Textbook of Rheumatology, Thirteenth and Fourteenth Editions, William J. Koopman, MD 14th:ISBN: 0-7817-2240-3, November 2000; Principles of Drug Development in Transplantation & Autoimmunity Landes Bioscience, ISBN:0412100614; Cancer & Autoimmunity by Gershwin M. et al.,ISBN: 0444503315 Elsevier Science ; *J Autoimmun* 2000 Jun; 14(4):278-82; The multi-functional ligands of the present invention, depending on their mode of administration (direct application by cannulating a lymphatic vessel or conventionally eg. intradermally or intravenously), can be advantageously employed to provide prolonged/strategic exposure to tolerance enhancing molecules (for example by employing a multivalent eg. bi-specific Ab fragment or diabody which has a first portion which binds to a lymph associated antigen and second portion which optionally comprises anti-idiotypic Ab portion mimicking the desired Ag or the antigen itself or a suitable portion thereof fused or conjugated to the first portion) on the intra-luminal surface of the lymphatic vessels, optionally, in addition to its conventional effects, when administered intradermally or intravenously, etc.. It is anticipated that the multi-functional ligands of the present invention would be useful to assess and/or effect tolerance induction (see Bassadona GP et al. *Proc Natl Acad Sci U S A* 1998 Mar 31; 95(7):3821-6; USP 6,106,834; USP 6,099,838; US6010902: Antibody heteroconjugates and bispecific antibodies for use in regulation of lymphocyte activity; as well as additional examples cited below with reference to examples of suitable anti-idiotypic antibodies).

The invention also contemplates using a multispecific contruct as described in WO99/37791.

It is contemplated that the present invention could be used to strategically mediate, CD45 (or variants/other PTPs) related "cell signaling", for example through signaling molecules (eg. inhibitors) using multifunctional ligands of the invention including but not limited to bispecific antibodies, antibody fusions/conjugates ie. where the immune affecting antibody portion or other moiety is conjugated, fused etc. to an antibody or fragment that binds to LYVE-1 (1999) Journal of Cell Biology Vol 144 No 4 p. 789-801) (see for example USP 5,914,111 Sievers EL, Cancer Chemother Pharmacol 2000 46 Suppl s18-22 WO9946268, Neel BG Curr Opin Immunol 1997 Jan 9(3) 405-420; Front Biosci 1998 Nov 1 3:D-1060-96, Slifka MK et al. J. Mol. Med 2000 78(2) 74-80 Goodnow CC Ciba Found Symp 1997 204: 190-202; Mustelin T. et al. Front Biosci. 1998 Nov 1; 3: D1060-96; Gaya A, Leuk Lymphoma, 1999 Oct 35 (3-4): 237-43; Sievers EL, Curr Opin Oncol. 2000 Jan 12(1): 30-5; Thomas ML, et al. Immul. Today 1999 Sep 20(9): 406-411; Appelbaum FR, Semin. Hematol. 1999 Oct; 36 (4 suppl. 6): 2-8; Ulyanova T; Immul. Res 1997 Feb; 16(1): 101-13; re PP32 for example USP 5,846,822 and Brody JR, et al. J Biol Chem. 1999 Jul 16; 274(29):20053-5 regarding the functional moiety of PP32 which is necessary for interaction with CD45, and for example USP 5,981,251 with respect to methods of identifying such molecules).

In preferred embodiments the invention is directed to multifunctional ligands that comprise immune function exerting moieties having functionalities of molecules currently in clinical trials or proposed for clinical trials (see for example Glennie MJ et al. Aug 2000, Immunology Today 408 Vol 21(8); see also Journal of Immunological Methods 237 (2000) 131-145; Mol Immunol 2000 Jun; 37(9) 515-526; Annu Rev Med 2001; 52:125-145; Annu Rev Med 2001 52:63-78; Q J Nucl Med 2000 Sep; 44(3) 268-83) including those that have an anti-CD2 functionality (see USP 5,795,572) anti-CD4 functionality (see for example USP 6,136,310 Herzyk D, J Infect Immun 2000 Feb; 69(2): 1032-1043) anti-CD3 functionality (for example WO 00/41474; WO 98139363; USP 6,113,901; Transplantation 2000 Dec 27 70 (12) 1707-12); Anti-CD44 functionality see for example Weiss L, et al., Proc Nat Acad Sci USA 2000; Jan 4 97(1) 285-290; Sugiyama K, Immunol Invest (1999) Mar-May 28(2-3) 185-200; Brocke S. et al. Proc Nat Acad Sci USA 1999 Jun 8 96(12) 6896; Mickeoz K et al. Nat Med 11995 Jun; 1(6); 558-63; Ahrens T et al., J Invest Dermatol. 2001 Jan116(1) 93-101); with respect to control of migration of T-cell lymphocytes see Nohara C, et al. J Immunol. 2001 Feb 1; 166(3) 2108-2115), anti-CD20 functionality (see Crit Rev Oncol Hematol 2001 Jan 37(1):13-25) etc. anti-CD22 functionality see for example Newton DL, et al. Blood 2001 Jan15; 97 (2): 528-535, USP 5,184,892; Anti-CD40/CTLA-4 see for example *J Immunol* 2000 Oct 1; 165(7):3612-9; Microsurgery 2000; 2c (8); 448-452; USP 5874082; USP

6056959; USP 5,801,227; USP 6004552; USP 5677165; USP 6087329; USP 5961974; USP 6051228; White CA,et al. Annu Rev Med. 2001; 52: 63-78 (see also reviews and specific applications referred to in Ditzel et al., Immunol Res. 2000; 21(2-3):185-93; USP 6,010,902, USP 5876950; USP 5876718; USP 5,601,819, USP 5981251, USP 5885579 and 5885796; *Cancer Immunol Immunother* 2000 Jun; 49(3):173-80; Omar K, J Neuroimmunol 2001 Feb 1, 113(1) 129-141; Bellido M, Eur J. Haematol 2001 Feb. 66(2) 100-106; Broeren et al. J Immunol (2000) Dec15 165(12) 6908-14; Alexandroff AB et al Mol Immunol 2000 June 37(9) 515-526; Werkerle T J Immunol. 2001 Feb 15 166(4) 2311-2316; Howard LM J Immunol 2001 Feb; 116(8) 1547-53 anti-CD154; *J Pharmacokinet Biopharm* 1999 Aug; 27(4):397-420, *J Clin Oncol* 2000 Apr; 18(8):1622-36, *Leukemia* 2000 Mar; 14(3):474-5, *Clin Cancer Res* 2000 Feb; 6(2):372-80, *Leukemia* 2000 Jan; 14(1):129-35, *J Nucl Med* 1999 Nov; 40(11):1935-46, *Blood* 1999 Nov 15; 94(10):3340-8, *Blood* 1999 Aug 15; 94(4):1237-47, *Cancer Res* 1999 May 1; 59(9):2096-101, *Vaccine* 1999 Apr 9; 17(15-16):1837-45, *Blood* 1998 Dec 1; 92(11):4066-71, *J Rheumatol* 1998 Nov; 25(11):2065-76, *Clin Pharmacol Ther* 1998 Sep; 64(3):339-46, *Mult Scler* 1996 Jul; 1(6):339-42, *Cancer Immunol Immunother* 1997 Jul; 44(5):265-72, *Transplant Proc* 1996 Dec; 28(6):3210-1, Arthritis Rheum. 1996 Jul; 39(7):1102-8, *Immunology* 1996 May; 88(1):13-9 and USP 5,876,718).

The invention contemplates assessment and therapeutic benefit of lymphatic localization in the case of toxic cross-reactivity of the second portion eg. antibody for its desired target with an undesired target (see eg. *Lancet* 1999 Nov 13; 354(9191):1691-5). It is contemplated that the toxic effect of a given immune affecting portion (second portion) of a multifunctional ligand of the invention, if permitted to have systematic distribution, could be avoided by confining its effects against cells passing through the lymphatic system and that heretofore (for this reason) unusable or failed target ligands due to their wide distribution on normal cells or proven toxic effects could be assessed in this lymphatic system localized context. Such other target ligands will be readily apparent to those skilled in the art.

The invention also contemplates that ligands or entities delivered to cells (the same or different entities) or preferably cooperative drug carrying entities can be cross-linked through complementary components such as biotin or avidin eg. cross-linking with avidin or streptavidin or a variant thereof, for example, *a biotin coated liposome* [or other micro/nano sphere, particle or drug carrying entity (including those adapted for slow release)] *containing a prodrug* and for example *a biotin coated liposome* [or other micro/nano sphere, particle or entity (including those adapted for slow release)] *containing the necessary pro-drug converting substance eg. enzyme* by delivering separately in succession an effective amount of complementary components, eg. a biotin type or biotin bearing component, preferably biotin or a functional variant thereof, sandwiched between the delivery two, avidin type or avidin bearing components, preferably avidin, streptavidin or a pharmaceutically acceptable variant thereof and/or by delivering as the avidin component two or more avidin (or variants thereof) subunits linked together by biotin or recombinantly fused together according to well known techniques in the art). Particularly in the case of a tumor targeting this strategy has the effect of prolonging whatever therapeutic effects or interactions are inherent in the therapetic moieties or drug carrying entities delivered to the cells. In particular, with respect to drug carrying enties, using for example an avidin or variant to link cooperating such entities together ensures that their contents are released in the same micro-environment. The avidin component or bearing component can also be delivered between the deliveries of the two biotin bearing components (see USP 6,077, 499, USP 5482698, USP 5846537, USP 6022951 and their cited references). Thus according to a preferred embodiment the invention is directed to a method of targeted delivery to a target cell of the contents of two cooperating drug carrying entities, preferably biotin coated liposomes, containing respectively preferably prodrug and prodrug to drug converting substance eg. enzyme, by administering a targeting ligand eg. an antibody which is biotin coated followed by an avidin or streptavidin or variants thereof, followed by the biotin coated liposomes, followed preferably by additional avidin to further anchor the cooperating components together.

Examples of bispecific antibodies that can be evaluated for adaptation to the invention or combination therapy therewith including those with an reasonable expectation of the therapeutic application and/or effectiveness, have been reviewed (see for example van Spriel AB, van Ojik HH, van De Winkel JG. Immunotherapeutic perspective for bispecific antibodies. Immunol Today. 2000 Aug; 21(8):391-7; Weiner LM. Bispecific antibodies in cancer therapy. Cancer J Sci Am. 2000 May; 6 Suppl 3:S265-71. Barbet J, Kraeber-Bodere F, Vuillez JP, Gautherot E, Rouvier E, Chatal JF. Pretargeting with the affinity enhancement system for radioimmunotherapy. Cancer Biother Radiopharm. 1999 Jun; 14(3):153-66. de Wolf FA, Brett GM. Ligand-binding proteins: their potential for application in systems for controlled delivery and uptake of ligands. Pharmacol Rev. 2000 Jun; 52(2):207-36.; Feuring-Buske M, Buske C, Unterhalt M, Hiddemann W. Recent advances in antigen-targeted therapy in non-Hodgkin's lymphoma. Ann Hematol. 2000 Apr; 79(4):167-74; Wang H, Liu Y, Wei L, Guo Y. Bi-specific antibodies in cancer therapyAdv Exp Med Biol. 2000; 465:369-80; Staerz UD, Lee DS, Qi Y. Induction of specific immune tolerance with hybrid antibodies. Immunol Today. 2000 Apr; 21(4):172-6; Hoefnagel CA. Nuclear medicine therapy of neuroblastoma. Q J Nucl Med. 1999 Dec; 43(4):336-43. Elsasser D, Stadick H, van de Winkel JG, Valerius T. GM-CSF as adjuvant for immunotherapy with bispecific antibodies. Eur J Cancer. 1999 Aug; 35 Suppl 3:S25-8. Molema G, Kroesen BJ, Helfrich W, Meijer DK, de Leij LF. The use of bispecific antibodies in tumor cell and tumor vasculature directed immunotherapy. J Control Release. 2000 Feb 14; 64(1-3):229-39. Bodey B, Bodey B, Siegel SE, Kaiser HE. Genetically engineered monoclonal antibodies for direct anti-neoplastic treatment and cancer cell specific delivery of chemotherapeutic agents. Curr Pharm Des. 2000 Feb; 6(3):261-76. Kudo T, Suzuki M, Katayose Y, Shinoda M, Sakurai N, Kodama H, Ichiyama M, Takemura S, Yoshida H, Saeki H, Seiiyo S, Takahashi J, Tominaga T, Matsuno S. Specific targeting immunotherapy of cancer with bispecific antibodies. Tohoku J Exp Med. 1999 Aug; 188(4):275-88. Koelemij R, et al. Bispecific antibodies in cancer therapy, from the laboratory to the clinic. J

Immunother. 1999 Nov; 22(6):514-24. Segal DM, Weiner GJ, Weiner LM Bispecific antibodies in cancer therapy Curr Opin Immunol. 1999 Oct; 11(5):558-62. Hudson PJ. Recombinant antibody constructs in cancer therapy. Curr Opin Immunol. 1999 Oct; 11(5):548-57. Kastenbauer E, Wollenberg B. [In search of new treatment methods for head-neck carcinoma]. Laryngorhinootologie. 1999 Jan; 78(1):31-5. Barth RF et al, Boron neutron capture therapy of brain tumors: an emerging therapeutic modality. Neurosurgery. 1999 Mar; 44(3):433-50; discussion 450-1.: Schirrmacher V, Haas C. Modification of cancer vaccines by virus infection and attachment of bispecific antibodies. An effective alternative to somatic gene therapy. Adv Exp Med Biol. 1998; 451:251-7. Fleckenstein G, Osmers R, Puchta J. Monoclonal antibodies in solid tumours: approaches to therapy with emphasis on gynaecological cancer, Med Oncol. 1998 Dec; 15(4):212-21. 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In another aspect the invention is directed to presenting antigen within the lymphatic system (eg. in the form of an anti-idiotype antibody) such as to facilitate a desired immune response eg. vaccination type responses). Optionally, adjuvants can be conventionally employed to assist initial immune stimulation eg. intradermally when appropriately delivered. Activating cytokines for example as specified above, can also be employed to enhance the immune response. Examples of antibodies having an anti-idiotypic counterpart or for which an anti-idiotypic counterpart could made by well known techniques in the art (and that are capable of exerting the desired anti-idiotypic effect) are numerous and numerous such antiidiotypic antibodies have application to immunization as well as applications relating to tolerance (see for example US patents: 6,146,627 Method for reducing T cell-mediated cytotoxicity in HIV using anti-idiotypic antibody; 6,132,718; Multi-stage cascade boosting vaccine; 6,117,427; 6,099,839 Gonococcal anti-idiotypic antibodies and methods compositions using them; 6,074,641 Gonococcal anti-idiotypic antibodies and methods and compositions using them ; 6,063,679 Anti-idiotypic monoclonal antibodies and compositions including the anti-idiotypic monoclonal antibodies; 6,060,049 Surrogate tolerogenesis for the development of tolerance to xenografts; 6,042,827Anti-idiotypic antibody induction of anti-tumor response; 6,007,815 Anti-idiotype vaccination against diseases resulting from pathogenic responses by specific T cell populations; 5,981,502 Methods and compositions for inducing apoptosis in tumor cells; 5,977,316 Monoclonal antibody 1A7 and related polypeptides; 5,977,315 Murine anti-idiotype antibody 3H1;

5,969,107Anti-idiotypic antibodies which induce an immune response against epidermal growth factor receptor 5,965,131 Delivery of diagnostic and therapeutic agents to a target site; 5,958,408 Delivery of diagnostic and therapeutic agents to a target site ; 5,939,067 Gonococcal anti-idiotypic antibodies and methods and compositions using them; 5,935,821 Polynucleotides related to monoclonal antibody 1A7 and use for the treatment of melanoma and small cell carcinoma; 5,888,509 Gonococcal anti-idiotypic antibodies and methods and compositions using them; 5,866,124 Antiidiotypic antibodies for high molecular weight-melanoma associated antigen; 5,858,361 Monoclonal anti-idiotypic anti-CA125 antibodies and pharmaceutical compositions containing them; 5,854,069 GD2 anti-idiotypic antibodies and uses thereof ; 5,849,583 Anti-idiotypic antibody and its use in diagnosis and therapy in HIV-related disease; 5,840,297 Vaccine comprising anti-idiotypic antibody to chlamydia GLXA and process; 5,817,513Anti ganglioside monoclonal antibodies; 5,808,005 Human carcinoma antigen; 5,798,100 Multi-stage cascade boosting vaccine; 5,792,455Anti-idiotypic antibody vaccines; 5,780,029 Antidiotypic monoclonal antibodies for treatment of melanoma; 5,766,588Tumor immunotherapy using anti-idiotypic antibodies; 5,744,135 Method of raising an immune response with an anti-idiotypic antibody having correspondence with human hepatitis B surface antigen; 5,728,812 Anti-idiotypic antibody composition for inhibiting acute complement-mediated cytotoxicity.

According to another aspect of the invention the multi-functional ligand comprises a first portion which binds to a lymph associated antigen and a second portion which binds to a tumor cell infected cell or infectious agent. This embodiment of the invention can be used for example, to assess and affect the ability of the tumor-binding portion to more advantageously inhibit metastasis. Optionally, for example, the portion which binds to a lymph associated antigen has a lower affinity and/or avidity so that the tumor cell binding portion preferentially binds to the tumor cell and is therefore more likely to accompany its passage through the lymphatic system. This strategy also has application to bi-specific antibodies of the invention in which the second portion is for example targeted to an immune cell. Optionally, multiple such muti-functional ligands may permit sufficient tumor cell anchoring to permit the tumor cell to be killed within the lymphatic system via a toxic payload carried by the multifunctional ligand or through the recruitment of immune cells which accomplish this end (eg using the same or a different multifunctional ligand fused or conjugated to a suitable cytokine (eg IL-2, IL-12). The prolonged presence of these cells could be advantageously used to assess methods of immunization directly against the tumor cell using, for example, cytokines including cytokines fused or conjugated in whole or functional part to a lymph targeted Ab on the same, or a different multifunctional ligand delivered in a suitable dose (with respect to generation of anti-tumor antibodies and other antibody fragments for application herein as well as important related technologies see also WO 00/50008; WO 01/01137; WO 97/37791; WO 99/37791; WO 97/10003; Hoogenboom et al. Nat. Biotechnology 15(2) Feb 1997 p125-126; Fell H. et al. Journal Of Immunolgy Vol 146(7) Apr 1991 p2446-2452; Anderson D. et al Bioconjugate Chemistry 14(1) Jan 1993 p10-18; USP 6, 172,197; USP 6,171,782; Immunological Investigations 2000 29(2) entire issue). Optionally the tumor binding portion internalizes and/or delivers a toxic payload, for example a radionuclide, or other toxin, or a cytokine to the tumor cell (with respect to selection of tumor internalizing human antibodies see for example Pool M et al. J Mol Biol. 2000 Sep 1; 301(5):1149-61, see also Kohl MD et al. J Mol. Biol. Biotechniques (2000) Vol 28(1) p162 In this way the multi-functional ligands of the invention, for example, when provided in a sufficient dose to both target the tumor and line a portion of the lymphatic system to which the target tumor is likely to drain, acts as a cancer treatment as well as a sentry system for assessing / augmenting (for example as an adjunct therapy) the ability of the tumor binding portion with/without payload to inhibit metastasis. There are numerous examples of functional cytokine and toxin fusions used for example in cancer therapy that may have application to the invention herein (for examples and reviews see references herein cited as well as WO 99/37791; WO99 53958A2 ENHANCEMENT OF ANTIBODY-CYTOKINE FUSION PROTEIN MEDIATED IMMUNE RESPONSES BY CO-ADMINISTRATION WITHPROSTAGLANDIN INHIBITOR; WO09730089A1 NOVEL ANTIBODY-CYTOKINE FUSION PROTEIN, AND METHODS OF MAKING AND USING THE SAME; WO00009150A2 CYTOKINE AND CYTOKINE RECEPTOR, AGONIST, ANTAGONIST AND/OR ANTIBODY COMBINATION FOR THERAPEUTIC ; WO00/06605A2 ; WO 99/52562A2 ENHANCEMENT OF ANTIBODY-CYTOKINE FUSION PROTEIN MEDIATED IMMUNE RESPONSES BY CO-ADMINISTRATION WITH ANGIOGENESIS INHIBITOR; WO 99/37791A1 MULTIPURPOSE ANTIBODY; Proceeding of the IBC's 11th Annual International Conference on Antibody Engineering State of the Art Science, Technology and Applications, December 3-6, 2000; Amplification of T cell-mediated immune responses by antibody-cytokine fusion proteins.Immunol Invest. 2000 May; 29(2):117-20; Cancer Res.1999 May 1; 59(9):2159-66.; Pharmacokinetics and stability of the ch14.18-interleukin-2 fusion protein in mice. Cancer Immunol Immunother. 1999 Aug; 48(5):219-29. Phase I study of single, escalating doses of a superantigen-antibody fusion protein (PNU-214565) in patients with advanced colorectal or pancreatic carcinoma. J Immunother. 2000 Jan; 23(1):146-53. Targeted toxin therapy for malignant astrocytoma.Neurosurgery. 2000 Mar; 46(3):544-51 (discussion @ 552); Targeting cytokines to tumors to induce active antitumor immune responses by recombinant fusion proteins. Hum Antibodies. 1999; 9(1):23-36; Lode HN, et al. Tumor-targeted IL-2 amplifies T cell-mediated immune response induced by gene therapy with single-chain IL-12. Proc Natl Acad Sci U S A. 1999 Jul 20; 96(15):8591-6; Gillies SD, et al. Improving the efficacy of antibody-interleukin 2 fusion proteins by reducing their interaction with Fc receptors. Cancer Res. 1999 May 1; 59(9):2159-66; Gan J, Kendra K, Ricci M, Hank JA, Gillies SD, Sondel PM. Specific enzyme-linked immunosorbent assays for quantitation of antibody-cytokine fusion proteins. Clin Diagn Lab Immunol. 1999 Mar; 6(2):236-42; Lode HN, et al. Synergy between an antiangiogenic integrin alphav antagonist and an antibody-cytokine fusion protein eradicates spontaneous tumor metastases. Proc Natl Acad Sci U S A. 1999 Feb 16; 96(4):1591-6.Weiner L. et al. Oncogene (2000) 19:6144-6151; Cancer Research 60 6434-6440 Nov 15 2000; Cancer Vaccines and Immunotherapy 2000 (textbook) ; Immunotherapy With Intravenous Immunoglobulins P. Imbach (1991) Academic Press; Molecular Approaches to

Tumor Immunotherapy (1997) World Scientific Publishing Company, Incorporated; Vaccines & Immunotherapy S. J. Cryz (1991) McGraw-Hill Ryerson, Limited *RE Internalizing antibodies* see eg Biological Effects of Anti-ErbB2 Single Chain Antibodies Selected for Internalizing Function.; Biochem Biophys Res Commun. 2001 Jan 12; 280(1):274-279 and references cited therein, Immunoconjugates of geldanamycin and anti-HER2 monoclonal antibodies: antiproliferative activity on human breast carcinoma cell lines J Natl Cancer Inst. 2000 Oct 4; 92(19):1573-81; Foulon CF, et al., Radioiodination via D-amino acid peptide enhances cellular retention and tumor xenograft targeting of an internalizing anti-epidermal growth factor receptor variant III monoclonal antibody. Cancer Res. 2000 Aug 15; 60(16):4453-60. Poul MA, Becerril B, Nielsen UB, Morisson P, Marks Selection of tumor-specific internalizing human antibodies from phage libraries J Mol Biol. 2000 Sep 1; 301(5):1149-61.Vrouenraets MB, et al.,Targeting of a hydrophilic photosensitizer by use of internalizing monoclonal antibodies: A new possibility for use in photodynamic therapy. Int J Cancer. 2000 Oct 1; 88(1):108-14.

In yet another aspect, the invention contemplates that the passage of tumor cells can be inhibited within the tumor vasculature using a bispecific ligand, optionally a bispecific antibody, which targets on the one hand a well known vascular endothelial marker and one the other hand binds to a ligand on the surface of the tumor. Other aspects of the invention related to tumor cell targeting are understood to described in reference to this aspect of the invention as well. It is also contemplated that markers which are present on both the lymphatic endothelium and the tumor vasculature can be simultaneously targeted with bispecific ligands of the invention to inhibit tumor metastasis and/or immunize a subject against tumor cells.

With respect to the use of immunocytokines for antibody therapy which have application to the invention herein see also Cytokine fusion improving the efficacy of antibody-interleukin 2 fusion proteins by reducing their interaction with Fc receptors. Cancer Res. 1999 May 1; 59(9):2159-66. Antibody-IL-12 fusion proteins are effective in SCID mouse models of prostate and colon carcinoma metastases. J Immunol. 1998 Jun 15; 160(12):6195-203. Amplification of T cell-mediated immune responses by antibody-cytokine fusion proteins. Immunol Invest. 2000 May; 29(2):117-20.

It is contemplated that the multifunctional ligands of the invention when used to inhibit metastasis, for example, in the manner described above, could be advantageously employed in combination with other well known therapies foe example cytoxic drugs, other tumor targeted antibodies and conjugates/fusions therewith used or currently being evaluate for immunotherapies, angiogenesis targeted drugs etc. (re angiogenesis see for example Angiogenesis in cancer and other diseases. Nature. 2000 Sep 14; 407(6801):249-57).

Similarly, a bi-specific antibody of the invention could be used to bind to antigens/ligands on lymphocytes which are known or become known to inhibit or enhance immune function or mediate a disease eg. CD45.

With respect to target receptors related to the inventions defined herein see also USP 6,277,962.

As discussed above, as used herein the term "lymph associated antigen" refers to antigens that are expressed significantly on lymphatic endothelial cells but not significantly expressed, if at all, on other tissues. Examples of such antigen include LYVE-1 a CD44 receptor analogue which binds to HA (February 22, 1999, Banerji et. al., Journal of Cell Biology Vol. 144, #4, p789-801) and which is expressed primarily on lymphatic endothelial cells. LYVE-1 specific antisera have been shown to inhibit binding of HA. The invention contemplates research and treatments using multi-functional ligands of the invention with respect to non-human mammals, including preferably agricultural animals, canine species, primates and mice having similar receptors/antigens. For example, a murine counterpart to LYVE-1 (published in Prevo R. et al. 2001 Feb 20, J. Biol. Chem.; Manuscript M011004200) can be employed to implement the various methods and embodiments described herein in a mouse model, for example to assess the extent of inhibition of metastasis effected by a multifunctional ligand (optionally comprising for example to a toxin, cytokine T cell receptor etc) which has a first portion which binds to LYVE-1 and a second portion which binds to, for example to GI-101, a breast tumor which is known to metastisize to the lung (see USP 6037520 and 5, 693, 533 see also US patents 5,643, 551, 5491284, 5569812, 5917124 and 6107540 and references cited in these patents, particularly with respect to other metastatic models and methods of evaluating anticancer drugs in mice). LYVE-1 counterparts in other mammals can be identified in the manner described by Prevo R. et al. (see also Skobe M. et al. Induction of tumor lymphangiogenesis by VEGF-C promotes breast cancer metastasis Nat. Med. Feb; 7(2) 192-8.)

Other models of metastasis in animals are well known in the art (see for example 1: Webb CP, Vande Woude GF.Genes that regulate metastasis and angiogenesis.J Neurooncol. 2000 Oct-Nov;50(1-2):71-87. 2: Chirgwin JM, Guise TA.Molecular mechanisms of tumor-bone interactions in osteolytic metastases.Crit Rev Eukaryot Gene Expr. 2000;10(2):159-78. 3: Rusciano D.Differentiation and metastasis in melanoma.Crit Rev Oncog. 2000;11(2):147-63. 4: Kobaek-Larsen M, Thorup I, Diederichsen A, Fenger C, Hoitinga MR.Review of colorectal cancer and its metastases in rodent models: comparativeaspects with those in humans.Comp Med. 2000 Feb;50(1):16-26. 5: Magnano M, Bongioannini G, Lerda W, Galvagno MB, Tondolo E, Canale G,Capogrosso B, Delsanto PP, Scalerandi M, Pescarmona GP.A physical-based model for the simulation of neoplastic growth and metastasis.J Surg Oncol. 2000 Jun;74(2):122-9. 6: Hoffman RM.Orthotopic metastatic mouse models for anticancer drug discovery and evaluation:a bridge to the clinic.Invest New Drugs. 1999;17(4):343-59. 7: Satyamoorthy K, Meier F, Hsu MY, Berking C, Herlyn M.Human xenografts, human skin and skin reconstructs for studies in melanoma development and progression.Cancer Metastasis Rev. 1999;18(3):401-5. 8: Fidler IJ, Schackert G, Zhang RD, Radinsky R, Fujimaki T.The biology of melanoma brain metastasis.Cancer Metastasis Rev. 1999;18(3):387-400. 9: Seftor RE,

Seftor EA, Hendrix MJ.Molecular role(s) for integrins in human melanoma invasion.Cancer Metastasis Rev. 1999;18(3):359-75. 10: Yoneda T.Cellular and molecular basis of preferential metastasis of breast cancer tobone.J Orthop Sci. 2000;5(1):75-81. 11: Morton DL, Chan AD.The concept of sentinel node localization: how it started.Semin Nucl Med. 2000 Jan;30(1):4-10. 12: Groom AC, MacDonald IC, Schmidt EE, Morris VL, Chambers AF.Tumour metastasis to the liver, and the roles of proteinases and adhesionmolecules: new concepts from in vivo videomicroscopy.Can J Gastroenterol. 1999 Nov;13(9):733-43. 13: Russo J, Russo IH.The pathway of neoplastic transformation of human breast epithelial cells.Radiat Res. 2001 Jan;155(1 Pt 2):151-154. 14: Uygur MC, Usubutun A, Ozen H, Ayhan A, Kendi S.Prognostic factors and the role of nephrectomy in metastatic renal cellcarcinoma.J Exp Clin Cancer Res. 1999 Sep;18(3):397-401. 15: Schlom J, Hodge JW.The diversity of T-cell co-stimulation in the induction of antitumor immunity.Immunol Rev. 1999 Aug;170:73-84. 16: Thames HD, Buchholz TA, Smith CD.Frequency of first metastatic events in breast cancer: implications forsequencing of systemic and local-regional treatment.J Clin Oncol. 1999 Sep;17(9):2649-58. 17: Allardyce RA.Is the port site really at risk? 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With respect to modifying an antibody to increase its affinity see also Crystal structure of Fab198, an efficient protector of the acetylcholine receptor against myasthenogenic antibodies. Eur J Biochem. 2001 Jul;268(13):3685-3693.

For example, in one embodiment the invention contemplates a bispecific antibody comprising an antigen binding component specific for a tumor cell associated antigen and a relatively low affinity anti-IL-6 receptor antibody component. With respect to the anti-tumor role of IL-6 see Wei LH et al. Interleukin-6 in cervical cancer: the relationship with vascular endothelial growth factor. Gynecol Oncol. 2001 Jul;82(1):49-56.

The invention contemplates that TCRs and modified TCRs (see for example, WO 01/48145) may be used as ligands, in place of antibody fragments for binding to target ligands such as peptide/MHC ligands.

Techniques for generating antibodies, and methods, for example of subtractive screening useful to identify other lymphatic vessel associated antibodies, including those optionally having smaller scFv, Fab and dAb (single domain antibody or functional fragment thereof) component (more easily passaging to lymphatic vessels from tissues particularly when constructed in the form of bispecific antibodies eg. diabodies etc.) by phage or ribosome display are well known in the art (see for example Hoogenbom HR et al. Immunol. Today (Aug. 2000) Vol 8 p 371; Schaffitzel C. et al. J Immunol. Methods (Dec. 10, 1999) 231(1-2) p. 119; Roberts RW et al. Curr Opin Chem Biol. 1999 Jun; 3(3):268-73; Winter G. et al. Annu Rev Immunol 1994 12:433-55; Kontermann RE et al. Nat Biotechnol. 1997 Jul; 15(7):629-31; Phage Display of Peptides and Proteins, A Laboratory Manual Kay BK et al. Eds 1996 Academic Press; Immunology Methods Manual Lefkovits, I ed. 1997 Academic Press; Hoogenboom et al. Immunotechnology 4 (1998)1-20; Kovar H. Ewing's sarcoma and peripheral primitive neuroectodermal tumors after their genetic union *Curr Opin Oncol* 1998 Jul; 10(4):334-42)

With respect to single domain antibodies see for example USP 5,824,520, USP 5622836, USP 5,702,892, USP 5,959,087, Unique single-domain antigen binding fragments derived from naturally occurring camel heavy-chain antibodies.J Mol Recognit. 1999 Mar-Apr; 12(2):131-40. An antibody single-domain phage display library of a native heavy chain variable region: isolation of functional single-domain VH molecules with a unique interface. J Mol Biol. 1999 Jul 16; 290(3):685-98 and references cited in these references.

Methods for making antibody fusion proteins and bi-specific antibodies including diabodies etc. and fusion proteins thereof are as well as uses pertinent for evaluation with this invention (including uses with a reasonable expectation of therapeutic application) also well established in the art (for reviews and particular applications see for example Adams GP et al. Journal of Immunological Methods 231 (1999) 249-260; USP 6,121,424, 6,027,725 and 6,025,165; EP 0654085; Hudson P. Exp. Opin. Invest. Drugs (2000) 9(6): 1231-1242; Antibody Fusion Proteins Steven M Chamow , Avi Ashkenazi Eds. ISBN 047118358X May 1999 Wiley; Antibody Engineering, Carl A. Borrebaeck Oxford University Press, 1995; Antibody Engineering:A Practical Approach David J. Chiswell, Hennie R. Hoogenboom, John McCafferty OxfordUniversity Press,1996; Antibody Engineering Protocols, Sudhir Paul (1995) Humana Press; Antibody Expression & Engineering (1998) Henry Y. Wang, Tadayuki Imanaka, American Chemical Society; Zhu Z. Biotechnology (NY) 1996 Feb.; 14(2): 192-6; Nielsen UB et al. Cancer Res. 2000 Nov 15; 60(22):6434-40; Lawrence LJ. Et al Febs Lett. 1998 Apr. 3; 425(3) 479-84; Hollinger et al., Cancer Immunol Immunother 1997 Nov-Dec 45 (3-4) 128-30; Immunotargeting of tumors: state of the art and prospects in 2000 Bull Cancer. 2000 Nov; 87(11):777-91; Helfrich Wet al Int. J. cancer 1998 Apr 13 76(2): 232-9; Wu AM, Q J Nuc Med. 2000 Sep.; 44(3):268-83 KrebsB. Et al. J Interferon cytokine Res 1998Sep 18(9): 783-91; Takemura Si, et al. Protein Eng. 2000 Aug.; 13(8): 583-8; Cochlovius B et al. J Immunol. 2000 Jul 15; 165(2):888-95; Atwell JL et al. Protein Eng. 1999 Jul; 12(7) : 597-604; kiprivanov SM et al. J. Mol Biol. 1999 Oct 15, 293 (1): 41-56; Alt M. et al FEBS LeH. Jul 2 454 ()1-2) 90-4. Hudson PJ et al. J Immunol Methods 1999 Dec 10; 231(1-2):177-89 Ardnt MA et al. Blood 1999 Oct 15 94(8): 2562-8; Lu D. et al. J Immunol. Methods 1999 Nov. 19; 230(1-2):159-171; Santos AD et al, Clin Cancer Res 1999 Oct 5 (10 suppl): 31185-31235 Kontermann RE et al. Nat Biotechnol. 1997 Jul; 15(7):629-31; Dolez et al. Protein eng. (2000) Aug 13 (8): 565-74; Adams GP et al. Nucl. Med. Biol (2000) May 27 (4); 339-46; Williams LE et al. Med phys 2000 may 27(5) 988-94; Fitzgerald K. Protein Eng 1997 oct 10(10): 1221-5 and the various references cited therein) as are various methods for identifying internalizing antibodies and creating toxin, radionuclide and cytokine fusions / conjugates (see ao Y et al Bioconj. Chem 1998 Nov-Dec; 9(6): 635-44) for fully exploiting various aspects of the invention herein defined (see for example Becerril B et al. Biochem Biophys Res Comm 1999 Feb 16; 255(2):386-93 see also additional references below. Triabodies and other known multivalent antibodies etc. (see for example Iliades P et al. FEBS Lett. 1997 June 16; 409(3):437-41) etc. could advantageously be employed to provide additional functionalities, as well as variation in avidity etc. for the purposes of variously exploiting the invention herein.

Methods of expressing and identifying new molecules like LYVE-1 are also well known in the art (see WO 98/06839)

Technologies for rendering the multifunctional ligands of the invention less immunogenic (eg such as employed by Biovation) are preferably applied to the multifunctional ligands of the invention.

For recent progress in the treatment of lupus nephritis see Zimmerman R. Annu Rev. Med. 2001; 52:63-78.

With respect to targeting Fas-L see US6068841:Antibodies to Fas-L for treatment of hepatitis.

The invention also contemplates using chemokines and variously targeted antibodies and fragments thereof fused or conjugated to chemokines or other molecules with for example, lymphocyte or other immune cell attractant properties (see for example Sun J. et al. Lymphology 32 (1999) 166-170; and Gerard C. et al. Nature Immunology (2001, Feb.) 2(2): p108; Immunological Reviews 1999 Vol 170 p.5-197) to attract immune cells into target tissues for eventual penetration into the lymphatic vessels for activation, signalling, binding to, inhibition, etc.. For example, for cancer treatment antibodies that bind to angiogenesis markers fused to such type such molecules eg. TNF-α can be advantageously employed optionally in conjunction with various vaccination strategies (including the use of the muti-functional ligands of the present invention) to attract immune cells including, optionally, vaccination-activated tumor targeting lymphocytes to the tumor site. In an indirectly related aspect (having independent applications as well as for combination therapy with a multifuctional ligand, the invention is also directed to an antibody that targets an angiogenesis marker fused/conjugated to a cytokine or antibody (ie a bispecific antibody) which binds to a cytokine, which cytokine augments adhesion of immune cells to blood vessels and method of using same (by administration to a subject), alone, in combination with multifunctional ligands of the invention or with other vaccination strategies to increase immune cell targeting to a solid tumor. In the case of a bispecific antibody it is contemplated that the cytokine binding portion has a relatively low functional affinity to the cytokine so as to compete unfavourably for its binding to its natural receptor.

With reference to modulating binding of leucocytes to endothelial adhesion molecules see for example US Patent No. 6,123,915 and the references therein cited.

It is well known to those in the art to make bispecific antibodies which are adapted to bind two different ligands on the same cell, for example so called antigen-forks as disclosed in USP 5,705,614 (see also Shi T et al. Murine bispecific antibody 1A10 directed to human transferrin receptor and a 42-kDa tumor-associated glycoprotein also

Clin Immunol Immunopathol 1996 Feb;78(2):188-95; Amoroso AR et al., Binding characteristics and antitumor properties of 1A10 bispecific antibody recognizing gp40 and human transferrin receptor Cancer Res 1996 Jan 1;56(1):113-20; Ring DB et al., Antigen forks: bispecific reagents that inhibit cell growth by binding selected pairs of tumor antigens, Cancer Immunol Immunother 1994 Jul;39(1):41-8; Lu D et al., Complete inhibition of vascular endothelial growth factor (VEGF) activities with a bifunctional diabody directed against both VEGF kinase receptors; fms-like tyrosine kinase receptor and kinase insert domain-containing receptor. Cancer Res 2001 Oct 1;61(19):7002-8; Schmiedl A, Breitling F, Dubel S. Expression of a bispecific dsFv-dsFv' antibody fragment in Escherichia coli.Protein Eng 2000 Oct;13(10):725-34 see also Park SS, et al., Generation and characterization of a novel tetravalent bispecific antibody that binds to hepatitis B virus surface antigens Mol Immunol 2000 Dec;37(18):1123-30; Kriangkum J et al., Bispecific and bifunctional single chain recombinant antibodies Biomol Eng 2001 Sep;18(2):31-40; USPs 4,474,893, 5,989,830; WO 00/29431).

With respect to antibodies to autoantigens, ADEPT, use of anti-eotaxin antibodies, DeImmunization, antibody-cytokine fusions, ribosome display, xenomouse technology; cutting edge phage display techniques, construction of *human* antibody fragment based phage display libraries, selection of internalizing antibodies by phage-display, cancer targeting antibodies, antibody arrays, plantibodies, design of mutant IGSF domains of CD2, CD58 and TCR; oligopeptide eg. paratope mimetics, diabodies, minibodies, triabodies, tetrabodies and related size/kinetics issues, caspase activatable pro-drugs, delivery of Bismeth-213 via scFv and diabodies,anti-angionenesis marker strategies, immunoenzype therapy of cancer (eg. with Rnases) pancarcinomic antigens like CEA (TAG")-72; and related technologies see the papers and references in Proceedings of IBC's 11th Annual International Conference on Antibody Engineering, State of the Art, Science, Technology and Applications Dec 3-6 2000 La Jolla, CA.

With respect to biology of the lymphatic system having practical application herein see Ikomi, F. lymphology (1999) 32:90-102; Shield JW. Lymphology 1999 32: 118-122 and Lymphology 33 (2000) 144-147, as well as the references cited therein.

The invention also contemplates control of such migration by inhibition of receptors that mediate such migration (see for example Sun J. et al. Lymphology 32 (1999) 166-170) for controlled application of the multifunctional ligands of the invention.

With respect to recent developments with respect to target ligands and/or immunotherapy having application herein see also WO 01/12224, WO 01/14550, WO 01/11059, WO 01/10205, WO 01/00679, WO029445A1:HUMANIZED ANTIBODY SPECIFIC FOR HUMAN 4-1BB AND PHARMACEUTICAL COMPOSITION COMPRISING SAME; WO 01/14885, WO/14564, WO 01/14558, WO 01/14224, WO 01/13945, WO 01/12840, WO 01/12781, Wo 01/12674, WO 01/12670, WO 01/12224, WO 01/12646; WO 01/12223, WO 01/12218, WO 01/12217, WO 01/12216, WO 01/12154, WO 01/14557, WO 01/11059, WO 01/10912, WO 01/11040, WO 01/10888, WO 01/10460, WO 01/10205, WO 01/09611, WO 01/09328, WO 01/09186, WO 01/09192, WO 01/08635, WO 01/07481, WO 01/07082, WO 01/07084, WO 01/07081, WO 01/07484, WO 01/07466, Triggering Fc alpha-receptor I (CD89) recruits neutrophils as effector cells for CD20-directed antibody therapy.J Immunol. 2000 Nov 15; 165(10):5954-61. CD47 engagement inhibits cytokine production and maturation of human dendritic cells.J Immunol. 2000 Feb 15; 164(4):2193-9.

The invention also contemplates that a multifunctional ligand that recognizes an immune cell as a target in virtue of a particular cell marker and will be able to deliver a toxic payload to the cell, for example, in virtue of its second portion comprising such toxic component fused or conjugated thereto. The invention also contemplates attracting or supplying other immune cells or molecules to kill, or otherwise inactivate the target immune cell (eg. lymphocytes eg. by TH cell modulation or CD4 cell modulation or using antibodies including anti-idiotypic antibodies. The invention therefore contemplates that treatment of such immune cells can be accomplished by a combination of different mechanisms or drugs depending on the disease so as to reduce immunosuppression due to immune cell ablation where this is the dominant consideration. Such interactions may require interaction with one or more ligands on the surface of the targeted immune cell, as facilitated via anchoring interactions of varying affinity/avidity/duration. The invention also contemplates using multifunctional ligands comprising or bound to selectins and ICAMs etc. to facilitate such targeting, for example co-adminstering same in a proportion which is for example 0.01% to 25% of the targeting multifunctional ligand. The relative amounts of the selectin/ICAM etc. (including antibody mimics) bearing multifunctional ligand as compared with the targeting multifunctional ligand can be determined empirically by varying the proportions and assessing any objective indicator of successful targeting in a disease related or purely experimental context. For example successful targeting (eg. antibody binding to eg. CD3, CD28, CD2) using multifunctional ligands of the invention could be monitored by evaluating levels of cytokines normally attributable to such binding (see for example CD8 T cell activation after intravenous administration of CD3 x CD19 bispecific antibody in patients with non-Hodgkin lymphoma. Cancer Immunol Immunother. 1995 Jun; 40(6):390-6. Definition of a lamina propria T cell responsive state. Enhanced cytokine responsiveness of T cells stimulated through the CD2 pathway. J Immunol. 1995 Jan 15; 154(2):664-75.

With respect to multifunctional ligands that are used to directly or indirectly exert an immunization function, other examples of disease associated peptides that can be presented as immunogens or inhibitor/modulators of immune activity or disease progression in one of the fashions suggested above include, examples as well as technologies referenced in, for example, knuth A, Cancer Chemother Pharmacol (2000); 46 suppl: 546-51; Engelhard VH, Cancer J Sci Am 2000 May; 6 Suppl 3: S272-80; Pietersz GA et al, Cell Mol Life Sci. 2000 Feb; 57(2): 290-

310; Algarra I et al, Hum Immunol. 2000 Jan; 61(1): 65-73; Tumour vaccines: a new immunotherapeutic approach in oncology.Ann Hematol. 2000 Dec; 79(12):651-9; Human tumor-rejection antigens and peptides from genes to clinical research Nippon Geka Gakkai Zasshi. 2000 Sep; 101(9):612-7. Pinilla-Ibarz J, Cathcart K, Scheinberg DA. CML vaccines as a paradigm of the specific immunotherapy of cancer. Blood Rev. 2000 Jun; 14(2):111-20).

In orderto present an MHC-peptide complex in proximity to a B7 co-stimulatory molecule, the invention contemplates using, in addition to varying amounts (varying from a 50/50 proportion) of adjacent multifunctional ligands (which may be a dAb, diabody etc.) preferably cross-linked by an avid in component, -- as a different strategy -- cross-linking with avidin or the like adjacent arms of a single diabody, triabody or tetrabody etc. which binds to or has been fused or conjugated individually to respective B7 and MHC peptide components (with respect to recombinant B7 and MHC molecules and fusion proteins thereof including antibody fusions and related technologies see references above and EP 99/97477 WO 99/42597, WO 97 28191, US 6, 197, 302, US6015884 US6140118, US 6,045,796, US 5580756, EP0935607, WO 9806749 WO9803552, EP 1054984, US 5869270, Construction and characterization of bispecific costimulatory molecules containing a minimized CD86 (B7-2) domain and single-chain antibody fragments for tumor targeting; method is useful for cancer therapy Rohrbach F et al.,Clin.Cancer Res.; (2000) 6, 11, 4314-22 WO 00/008057 17 Feb 2000; WO 9921572 6 May 1999; WO 9913095 18 Mar 1999; WO 9742329 13 Nov 1997; WO 9720048 5 Jun 1997; WO 9640915 19 Dec 1996; WO 00/023087; EP 610046 10 Aug 1994, USP 6056952 as well as references therein cited).

In a related aspect, the invention similarly contemplates using or more antibodies (optionally biotinylated and cross-linked by an avidin component) that bind to the same or different epitopes on a tumor including, where two such antibodies are used different proportions of MHC and B7 linked (ie fused, conjugated or capable of binding to) antibodies as well as different proportions of different epitope-specific antibodies to optimize the distribution of such cross-linked B7 and MHC peptide complexes for T-cell recognition. In this way any strongly immunogenic peptide may be used in conjunction with suitable vaccination strategies to create a universal cancer antigen. Using a tumor unrelated peptide is advantageous to avoid any tolerization effects resulting from T-cell binding to the MHC-peptide alone and does not preclude immune system recognition of a different epitope or other therapies. In a preferred embodiment, a single multifunctional ligand or pair of multifunctional ligands optionally biotinylated and cross-linked by an avidin (or variants), is used to bind to both the lumen of the lymphatic system and to a tumor cell. (using for example a trispecific antibody with monovalent linkage to both the cancer cell and lymphatic endothelial cell and a third antibody component having respective fusions to one of MHC-peptide and B7 on heavy and light chain, or a trispecific or tetraspecific tetrabody having an antibody component devoted to each or the B7 and MHC linkages). This permits a single molecule to be used for both the immunization within the lymphatic system and the tumor targeted antigen display. However, it will be appreciated that presentation of MHC-peptide complex on a tumor does not necessarily require costimulatory B7 presentation to induce a cytotoxic T cell response which is specific for the peptide and that multiple such presentations, preferably in a cross-linkable fashion may be preferable. Accordingly, strategies herein for costimulatory presentation of MHC-peptide and B7 may be differently applied to a lymphatic endothelial cell surface for immunization purposes and and a tumor cell surface (primarily for recognition purposes), for example by using avidin facilitated cross-linking of in the former but not the latter (tumor) context or using different sets of molecules in each case or using modularly reconstructing the tumor cell suface with a bispefic antibody that binds to a separately administered MHC and/or B7 component.

Subject to the latter proviso, in preferred embodiments, the invention contemplates using as separate counterparts 1) separate trispecific Abs, each including for example, one antibody component which binds to the each of the respective B7 and MHC molecules which are preferably together, separately administered. Such multifunctional ligands are preferably biotinylated for cross-linking – both between adjacent trispecific Abs and adjacent T-cell stimulatory/co-stimulatory arms; or 2) separate bispecific pairs of Abs each respectively having 1) either a B7 and lymphatic vessel or B7 and tumor binding portion or 2) a MHC peptide complex and a lymphatic vessel or MHC complex and tumor binding, portions which again are prefereably cross-linked by an avidin,streptavidin or a variant (ie. using biotinylated antibodys) This latter embodiment permits smaller size antibody molecules to be used for better tumor targeting. Antibody components which recognize the non-T cell interactive portion of the B7 or MHC molecule can be readily generated by phage display, for example in the case of a known peptide specific antibody to an MHC peptide complex (see Chames et al. Proc Natl Acad Sci USA 97, 7969 and Chames et. al. "Affinity Maturation of TCR-Like MHC-peptide specific antibody: peptide specificity is possible over a wide affinity range" Proceedings of IBC Conference on Antibody Engineering Dec. 2000] eg. by first causing binding of the "peptide specific" antibody and then doing the phage display eg. using an array of multiple (eg. repeats of the same antibody) such peptide specific MHC antibodies, applying the MHC peptide complex to effect binding and then performing the phage or ribosome display. Alternatively a TCR (eg cell bound) or analogue/mimotope could be used for the orientation. Similarly antibodies could be generated which in effect do not compete with CD28 or a mimotope thereof to create suitable anti-B7 type antibodies. Anti-B7 antibodies are known in the art. The invention also contemplates that the MHC-peptide binding function may be supplied using a linked superantigen (US 6197299, WO 9601650 25 Jan 1996; Proc.Natl.Acad.Sci.U:S.A.; (1994) 91, 19, 8945-49) in both the tumor and lymphatic system binding sites. Optionally, the tumor antigen or one or both of the antigens are a pan-carcinomic antigen like TAG-72, CEA, H11 (WO 97/44461). The invention also contemplates using one or more phage display libraries to optimize the development of MHC/B7 costimulatory bispecific antibodies, by using cell sized latex spheres coated with an antigen eg. CEA in various surface dispersions (or a cell) and using a array of preferably biotinylated antibodies which recognize the antigen and have a "oppositely located"portion fused, conjugated or capable of binding to one or both of MHC and B7, the library optionally also presenting also

variations and combinations of lengths (truncations) of one or more constant regions or for example the CDR2 generated by phage display, depending on the choice of antibody, and with microarray technology, using a signalling means to detect T-cell recognition and evaluating cytotoxicity with for example a Cr51 release assay. (with respect to protein chip or microarray technology see WO 00/63701 references, for example in the Proceedings of IBC's conference on Protein Microarray Technology March 19-21 Santiago California.

The invention also contemplates use of recently published antibodies in the context of the invention (see WO 01/19861, WO 01/19990, WO 01/19860, WO 01/19987, WO 01/19990, WO 99/58678, WO 00/59943, WO 01/18014, WO 01/18016, WO 01/18204, WO 01/18042, WO 01/18021, WO 01/18014, WO 01/18046, WO 01/16166, WO 01/15731, WO 01/15728, WO 01/16183, WO 01/16170, WO 01/15732.

The invention is also directed to a method of evaluating dosing, ligand saturation, avidity effects of simultaneous ligand binding on prolonged anchoring and associated benefits (eg. to delay a cancer cell for targeted killing or facilitate transfer of the multifunctional ligand to the targeted cell), cooperative interactions, cross-linking interactions (see *J Immunol* 2001 Mar 1; 166(5):3256-3265; Nippon Rinsho. 1999 Dec; 57 Suppl:428-32; Harefuah. 2000 Jun 15; 138(12):1046-50. Leuk Lymphoma. 1998 Mar; 29(1-2):1-15) and costimulatory interactions by administering to a test subject two different multifunctional ligands of the invention with cooperating second portions.

With respect to the display of functional peptides on an antibody type scaffold see Nuttal SD; et al:, Proteins (1999) 36: 217-227; see also Skerra A., J. Mol. Recognition 2000 July-Aug 13(4): 167-187. The invention also contemplates bispecific multifunctional ligands in which the immune function exerting moiety exerts its function through binding to an immunogenic component or carrier for such component as discussed above, for example an Fc domain fused to a peptide, a heat shock protein (see for example Wang XY, Immunol Invest 2000 May 29(2): 131-7 and references cited therein as well as US6168793; US6071956 ; US05981706; US05948646 Methods for preparation of vaccines against cancer comprising heat shock protein-peptide complexes; US05830464 Compositions and methods for the treatment and growth inhibition of cancer using heat shock/stress protein-peptide complexes in combination with adoptive immunotherapy as well as patents, scientific articles and patent applications referenced in these patents; with respect to MHC peptide complexes(see for example WO 99/64597, WO 98/03552, WO 98/06749 and references cited therein).

As described above, the invention also contemplates that the lower affinity ligand binding arm of the aforementioned multifunctional ligand (ie. having a high affinity targeting arm and a lower affinity effector arm) is constituted by a high affinity ligand, for example an high affinity antibody or functional fragment thereof, which binds to a target biological effector (eg. a cytokine, chemokine, growth factor, hormone or other biological response modifier or drug) with high affinity, in a manner which permits the effector to continue to bind to its desired target receptor while bound to the antibody (ie. the antibody binds to a portion of the effector which is not critically involved in the effector binding to its receptor) provided that when bound to the effector the antibody or fragment thereof has, when combined with the effector, a suitably lower affinity for the receptor than the ligand binding arm which functions as the high affinity binder has for its target cell marker. In one embodiment the binding moiety which binds to the biological effector binds to it with higher affinity than the affinity that the effector has for the effector receptor. The invention also contemplates that this binding arm can bind to biological effector in a manner which permits it to bind to one receptor but not a related receptor to which the effector would otherwise bind (see examples below). The invention also contemplates that antibody arrays are used to screen for antibodies which are capable of binding to such biological effectors, while bind in situ to their receptors. The invention also contemplates that such binders, when bound to the biological effector, can be used to test their ability to bind to related receptors, such as those within the same family eg. within the same family of TNF like receptors. With respect to antibody microarrays see for example Cahill DJ.Protein and antibody arrays and their medical applications.J Immunol Methods. 2001 Apr;250(1-2):81-91. MacBeath G. Proteomics comes to the surface.Nat Biotechnol. 2001 Sep;19(9):828-9. Clewley JP.Recombinant protein arrays.Commun Dis Public Health. 2000 Dec;3(4):311-2; Holt LJ, Enever C, de Wildt RM, Tomlinson IM. The use of recombinant antibodies in proteomics.Curr Opin Biotechnol. 2000 Oct;11(5):445-9. Walter G, et al.Protein arrays for gene expression and molecular interaction screening.Curr Opin Microbiol. 2000 Jun;3(3):298-302. de Wildt RM, Mundy CR, Gorick BD, Tomlinson IM.Antibody arrays for high-throughput screening of antibody-antigen interactions.Nat Biotechnol. 2000 Sep;18(9):989-94.Holt LJ, et al.By-passing selection: direct screening for antibody-antigen interactions using protein arrays. Nucleic Acids Res. 2000 Aug 1;28(15):E72 and the references cited therein. The term receptor as used herein for greater certainty includes decoy receptors. Examples of decoy receptors includeTRAIL decoy receptors (APO-2L), CD44 decoy like receptors (hyaluronan), interleukin receptor like protein (IL-17) (see J Biol Chem 2001 Nov 12), CD95-Fc decoy receptor, TRAMP, IL-1 RII receptor, osteoprotegerin (OPG), IL13Ralpha2.

With respect to affinity maturation see for example Cole G, Hudson PJ, Irving RA.Protein affinity maturation in vivo using E. coli mutator cells.J Immunol Methods. 2001 May 1;251(1-2):187-93.Manivel V, Sahoo NC, Salunke DM, Rao KV.Maturation of an antibody response is governed by modulations in flexibility ofthe antigen-combining site.Immunity. 2000 Nov;13(5):611-20.Boder ET, Midelfort KS, Wittrup KD.Directed evolution of antibody fragments with monovalent femtomolarantigen-binding affinity.Proc Natl Acad Sci U S A. 2000 Sep 26;97(20):10701-5.Holler PD, Holman PO, Shusta EV, O'Herrin S, Wittrup KD, Kranz DM.In vitro evolution of a T cell receptor with high affinity for peptide/MHC.Proc Natl Acad Sci U S A. 2000 May 9;97(10):5387-92.Daugherty PS, Chen G, Iverson BL, Georgiou G.Quantitative analysis of the effect of the mutation frequency on the affinity

maturation of single chain Fv antibodies.Proc Natl Acad Sci U S A. 2000 Feb 29;97(5):2029-34.VanAntwerp JJ, Wittrup KD.Fine affinity discrimination by yeast surface display and flow cytometry.Biotechnol Prog. 2000 Jan-Feb;16(1):31-7.Adams GP, Schier R.Generating improved single-chain Fv molecules for tumor targeting.J Immunol Methods. 1999 Dec 10;231(1-2):249-60. Review.Daugherty PS, Chen G, Olsen MJ, Iverson BL, Georgiou G.Antibody affinity maturation using bacterial surface display.Protein Eng. 1998 Sep;11(9):825-32.Wong YW, Kussie PH, Parhami-Seren B, Margolies MN.Modulation of antibody affinity by an engineered amino acid substitution.J Immunol. 1995 Apr 1;154(7):3351-8.Balint RF, Larrick JW.Antibody engineering by parsimonious mutagenesis.Gene. 1993 Dec 27;137(1):109-18. Schillbach JF, Near RI, Bruccoleri RE, Haber E, Jeffrey PD, Novotny J,Sheriff S, Margolies MN.Modulation of antibody affinity by a non-contact residue.Protein Sci. 1993 Feb;2(2):206-14.Chames P, Baty D. Engineering of an anti-steroid antibody: amino acid substitutions changeantibody fine specificity from cortisol to estradiol.Clin Chem Lab Med. 1998 Jun;36(6):355-9. Kussie PH, Parhami-Seren B, Wysocki LJ, Margolies MN.A single-engineered amino acid substitution changes antibody fine specificity. J Immunol. 1994 Jan 1;152(1):146-52, as well as references cited therein.

With respect to generation of high affinity antibodies and affinity maturation of antibodies see also Hanes J. Nat. Biotechnol. 2000 Dec; 18(12): 1287-92; references in Hudson PJ Exp. Opin. Invest. Drugs (2000) 9(6) 1231-1242; Toran JL et al Evr. J. Immunol. 2001 Jan; 31(1) 128-137. Nielson VB et al. Cancer Res 2000 Nov 15; 60 (22) 6434-40 Adams Gp, Journal of Immunological Methods (1999) 249-260; Chowdhury PS et al (June 1999) Nature Biotechnology Vol 17 p. 568

With respect to strategies and recent technologies which have application to the invention see references in Hudson PJ Exp. Opin. Invest. Drugs (2000) 9(6) 1231-1242 and in particular references relating to strategies to achieve multivalency and multispecificity; recruitment of viruses, ADEPT, photoactivation of cytotoxic radionuclides; surface receptor cross-linking; (see also Eur. J. Immunol 2000 30(10) 3006); use of anti-B antibodies; immunocytokines (see also Lode HN Immul. Res. 2000, 21 (2-3) 279-88; Gillies SD Cancer Research 59 2159-2166 May 1999; Lode HN et al Drugs of Today 2000 36(5) 3221-336).

With respect to practicial size limitations and pharmacokinetics of various types of antibodies and fragments see Colcher D. et al. G.J. Nucl. Med (1999) 43: 132-139; Wu AM et al G.J. Nucl. Med 2000 Sep; 44(3): 268:83; Williams LE et al Med Phys 2000 May 27(5): 988-941 Ikomi F lymphology 32 (1999) 90-102.

With respect to the construction of diabodies see also Takemura Si et al. Protein Eng. 2000 Aug;13(8) 583-8; Biomol. Eng. 2001 Sept;18(2):31-40.

With respect to anti-cancer antibodies see also 6,180,357.

With respect to technologies to produce multivalent and/or multispecific antibodies see also USP 6, 172, 197; WO 92/01047; WO 93/11161; WO 94/07921; WO 94/13804; Helfrich W. et al. Journal of Immunological Methods 237 (2000) 131-145. Proceedings of 11th IBC Conference on Antibody Engineering; WO 01/85795

Monoclonal antibodies may be routinely produced as taught by Harlow, E. and D. Lane, (1988) ANTIBODIES: A *Laboratory Manual,* Cold Spring Harbor Laboratory, Cold Spring Harbor N.Y. Humanized antibodies may be routinely produced as taught, for example, by U.S. Pat. No. 5,585,089 and U.S. Pat. No. 5,530,101. Techniques for engineering antibodies are well known and described in Winter and Millstein (1991) Nature 349:293; and Larrich and Fry (1991) Hum. Antibod. and Hybridomas 2:17. One having ordinary skill in the art may use well known techniques and starting materials and/or commercially available expression vectors and systems that are readily available and known in the art. See e.g., Sambrook et al., Molecular Cloning a *Laboratory Manual,* Second Ed. Cold Spring Harbor Press (1989).

Examples of radionuclides useful as toxins in radiation therapy are well known. Some examples are referred to below. Auger emitters may be preferred for internalizing antibodies. As suggested above, the term antibody is used interchangeably with antibody fragment and antigen binding fragment and includes a whole antibody; antibody fragment a portion of an antibody such as a scFV F(ab') 2 F(ab) 2, Fab', Fab, dAb, microbodies (WO0029004A1:SMALL FUNCTIONAL UNITS OF ANTIBODY HEAVY CHAIN VARIABLE REGIONS) or the like or multivalent such fragments, including those itemized or referenced herein. Regardless of structure, an antibody fragment can be made to bind with the same antigen that is recognized by the intact antibody. More particularly, in addition to fragments formed by enzymaic digestion of an intact Ab the term antibody or "antibody fragment" unless otherwise stated also includes any synthetic or genetically engineered protein that acts like an antibody by binding to a specific antigen to form a complex including/as applicable, cysteine noose peptides and minimal recognition units consisting of the amino acid residues that mimic the hypervariable region. Although fully human antibodies, for example, antibodies generated via human-human hybridomas or through phage display using human

antibody based libraries, are preferred, the invention does not preclude other strategies to avoid a HAMA type response.

A chimeric antibody is a recombinant protein that contains the variable domains and complementary determining regions derived from, for example, a rodent antibody, while the remainder of the antibody molecule is derived from a human antibody.

With respect to stability engineering of scFv fragments for enhanced mulfunctional ligands comprising scFvs see *J Mol Biol* 2001 Feb 2; 305(5):989-1010.

Humanized antibodies are recombinant proteins in which murine LDR's of a monoclonal antibody have been transferred from heavy and light variable chains of the murine immunoglobulin into a human variable domain.

The term therapeutic agent as used herein, is a molecule or atom which is conjugated etc. to an antibody moiety to produce combination including a conjugate which is useful for therapy. Examples of therapeutic agents include drugs, toxins, immunomodulators, chelators, boron compounds, photoactive agents or dyes, and radioisotopes.

The term "a naked antibody" may be used to refer specifically to an entire antibody, as opposed to an antibody fragment, which is not conjugated with a therapeutic agent. Naked antibodies include both polyclonal and monoclonal antibodies, as well as certain recombinant antibodies, such as chimeric and humanized antibodies.

The term immunoconjugate may be used to refer a conjugate of an antibody component with a therapeutic agent.

As used herein, the term antibody fusion protein refers to a recombinant molecule that comprises an antibody component and a second functional component for example a therapeutic agent. Examples of therapeutic agents suitable for such fusion proteins include immunomodulators ("antibody-immunomodulator fusion protein") and toxins ("antibody-toxin fusion protein").

Production of Antigen - Specific Monoclonal Antibodies, Rodent monoclonal antibodies to antigen can be obtained by methods known to those skilled in the art. See generally, for example, Kohler and Milstein, Nature 256:495 (1975), and Coligan et al. (eds.), Current Protocols in Immunology, Vol. 1, pages 2.5.1-2.6.7 (John Wiley & Sons 1991) ["Coligan"]. Briefly, monoclonal antibodies can be obtained by injecting mice with a composition comprising the antigen in a question (Ag), verifying the presence of antibody production by removing a serum sample, removing the spleen to obtain B-lymphocytes, fusing the B-lymphocytes with myeloma cells to produce hybridomas, cloning the hybridomas, selecting positive clones which produce anti-Ag antibodies, culturing the clones that produce antibodies to the antigen, and isolating the antibodies from the hybridoma cultures. Transgenic mice having for example engineered immune systems to create human antibodies such those used by Medarex and Abgenix are also contemplated for use herein to create suitably targeted antibodies.

Monoclonal antibodies can be isolated and purified from hybridoma cultures by a variety of well-established techniques. Such isolation techniques include affinity chromatography with Protein-A Sepharose, size-exclusion chromatography, and ion-exchange chromatography. See, for example, Coligan at pages 2.7.1-2.7.12 and pages 2.9.1-2.9.3. Also, see Baines et al., "Purification of Immunoglobulin G (IgG) ," in Methods in Molecular Biology, Vol. 10, pages 79-104 (The Humana Press, Inc. 1992).

With respect to relevant molecular biology techniques See also, for example, Ausubel et al., (eds.), CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, pages 8.2.8 to 8.2.13 (1990) ["Ausubel"]. Also, see Wosnick et al., Gene 60:115 (1987); and Ausubel et al. (eds.), Short Protocols in Molecular Biology, 3rd Edition, pages 8--8 to 8-9 (John Wiley & Sons, Inc. 1995). Established techniques using the polymerase chain reaction provide the ability to synthesize genes as large as 1.8 kilobases in length. Adang et al., Plant Molec. Biol. 21:1131 (1993) Bambot et al., PCR Methods and Applications 2:266 (1993); Dillon et al., "Use of the Polymerase Chain Reaction for the Rapid Construction of Synthetic Genes," in Methods in Molecular Biology, Vol. 15: PCR Protocols: Current Methods and Applications, White (ed.), pages 263-268, (Humana Press, Inc. 1993).

Techniques for constructing chimeric antibodies are well-known to those of skill in the art. As an example, Leung et al., Hybridoma 13:469 (1994

In yet another embodiment, an antibody of the present invention is a "humanized" monoclonal antibody. That is, mouse complementarity determining regions are transferred from heavy and light variable chains of the mouse immunoglobulin into a human variable domain, followed by the replacement of some human residues in the framework regions of their murine counterparts. Humanized monoclonal antibodies in accordance with this invention are suitable for use in therapeutic methods. General techniques for cloning murine immunoglobulin variable domains are described, for example, by the publication of Orlandi et al., Proc. Nat'l Acad. Sci. USA 86: 3833 (1989). Techniques for producing humanized monoclonal antibodies are described, for example, by Jones et al., Nature 321:522 (1986), Riechmann et al., Nature 332:323 (1988), Verhoeyen et al., Science 239:1534 (1988), Carter et al., Proc. Nat'l Acad. Sci. USA 89:4285 (1992), Sandhu, Crit. Rev. Biotech. 12:437 (1992), and Singer et al., J. Immun. 150:2844 (1993). The publication of Leung et al., Mol. Immunol. 32:1413 (1995), describes the construction of humanized LL2 antibody.

In a preferred embodiment of the invention the multifunctional ligand has a unique portion which differentiates it from other antibodies and preferably other co-administered different multifunctional ligands, which unique portion, allows the multifunctional ligand to be efficiently segregated on an immunoaffinity column. In the case of differentiating a single multifunctional ligand an anti-idiotype (assuming the first portion consists of an antibody) or other antibody uniquely recognizing the first portion could be employed. Modifying a portion of the first portion, for example in the case where it is antibody component and creating a antibody thereto, for example by phage display, is a matter of routine skill in the arts of antibody engineering and phage display.

In another embodiment, an antibody of the present invention is a human monoclonal antibody. Such antibodies are obtained from transgenic mice that have been "engineered" to produce specific human antibodies in response to antigenic challenge. In this technique, elements of the human heavy and light chain locus are introduced into strains of mice derived from embryonic stem cell lines that contain targeted disruptions of the endogenous heavy chain and light chain loci. The transgenic mice can synthesize human antibodies specific for human antigens, and the mice can be used to produce human antibody-secreting hybridomas. Methods for obtaining human antibodies from transgenic mice are described by Green et al., Nature Genet. 7:13 (1994), Lonberg et al., Nature 368:856 (1994), and Taylor et al., Int. Immun. 6:579 (1994).

Examples of Production of Antibody Fragments

Antibody fragments can be prepared, for example, by proteolytic hydrolysis of an antibody or by expression in E. coli of the DNA coding for the fragment.

Antibody fragments can be obtained by pepsin or papain digestion of whole antibodies by conventional methods. For example, antibody fragments can be produced by enzymatic cleavage of antibodies with pepsin to provide a 5 S fragment denoted $F(ab')_2$. This fragment can be further cleaved using a thiol reducing agent, and optionally a blocking group for the sulfhydryl groups resulting from cleavage of disulfide linkages, to produce 3.5 S Fab' monovalent fragments. Alternatively, an enzymatic cleavage using pepsin produces two monovalent Fab fragments and an Fc fragment directly. These methods are described, for example, by Goldenberg, U.S. Pat. Nos. 4,036,945 and 4,331,647 and references contained therein. Also, see Nisonoff et al., Arch Biochem. Biophys. 89:230 (1960); Porter, Biochem. J. 73:119 (1959), Edelman et al., in Methods in Enzymology Vol 1, page 422 (Academic Press 1967), and Coligan at pages 2.8.1-2.8.10 and 2.10.-2,10.4.

Other methods of cleaving antibodies, such as separation of heavy chains to form monovalent light-heavy chain fragments, further cleavage of fragments, or other enzymatic, chemical or genetic techniques may also be used, so long as the fragments bind to the antigen that is recognized by the intact antibody.

For example, Fv fragments comprise an association of V_H and V_L chains. This association can be noncovalent, as described in Inbar et al., Proc. Nat'l Acad. Sci. USA 69:2659 (1972). Alternatively, the variable chains can be linked by an intermolecular disulfide bond or cross-linked by chemicals such as glutaraldehyde. See, for example, Sandhu, supra.

Preferably, the Fv fragments comprise V_H and V_L chains which are connected by a peptide linker. These single-chain antigen binding proteins (scFv) are prepared by constructing a structural gene comprising DNA sequences encoding the V_H and V_L domains which are connected by an oligonucleotide. The structural gene is inserted into an expression vector which is subsequently introduced into a host cell, such as E. coli. The recombinant host cells synthesize a single polypeptide chain with a linker peptide bridging the two V domains. Methods for producing scFvs are described, for example, by Whitlow et al., Methods: A Companion to Methods in Enzymology 2:97 (1991). Also see Bird et al., Science 242:423 (1988), Ladner et al., U.S. Pat. No. 4,946,778, Pack et al., Bio/Technology 11:1271 (1993), and Sandhu, supra.

Another form of an antibody fragment is a peptide coding for a single complementarity-determining region (CDR). CDR peptides ("minimal recognition units") can be obtained by constructing genes encoding the CDR of an antibody of interest. Such genes are prepared, for example, by using the polymerase chain reaction to synthesize the variable region from RNA of antibody-producing cells. See, for example, Larrick et al., Methods: A Companion to Methods in Enzymology 2:106 (1991); Courtenay-Luck, "Genetic Manipulation of Monoclonal Antibodies," in Monoclonal Antibodies: Production, Engineering and Clinical Application, Ritter et al. (eds.), pages 166-179 (Cambridge University Press 1995); and Ward et al., "Genetic Manipulation and Expression of Antibodies," in Monoclonal Antibodies: Principles and Applications, Birch et al., (eds.), pages 137-185 (Wiley-Liss, Inc. 1995).

5. Preparation of Immunoconjugates

The present invention contemplates immunoconjugates to assess and effect treatment of various disease conditions. Such immunoconjugates can be prepared by indirectly conjugating a therapeutic agent to an antibody component. For example, general techniques are described in Shih et al., Int. J. Cancer 41:832-839 (1988); Shih et al., Int. J. Cancer 46:1101-1106 (1990); and Shih et al., U.S. Pat. No. 5,057,313. The general method involves reacting an antibody component having an oxidized carbohydrate portion with a carrier polymer that has at least one free amine function and that is loaded with a plurality of drug, toxin, chelator, boron addends, or other therapeutic agent. This reaction results in an initial Schiff base (imine) linkage, which can be stabilized by reduction to a secondary amine to form the final conjugate.

The carrier polymer is preferably an aminodextran or polypeptide of at least 50 amino acid residues, although other substantially equivalent polymer carriers can also be used. Preferably, the final immunoconjugate is soluble in an aqueous solution, such as mammalian serum, for ease of administration and effective targeting for use in therapy. Thus, solubilizing functions on the carrier polymer will enhance the serum solubility of the final immunoconjugate. In particular, an aminodextran will be preferred.

The process for preparing an immunoconjugate with an aminodextran carrier typically begins with a dextran polymer, advantageously a dextran of average molecular weight of about 10,000-100,000. The dextran is reacted with an oxidizing agent to effect a controlled oxidation of a portion of its carbohydrate rings to generate aldehyde groups. The oxidation is conveniently effected with glycolytic chemical reagents such as NaIO.sub.4, according to conventional procedures.

The oxidized dextran is then reacted with a polyamine, preferably a diamine, and more preferably, a mono- or polyhydroxy diamine. Suitable amines include ethylene diamine, propylene diamine, or other like polymethylene diamines, diethylene triamine or like polyamines, 1,3-diamino-2-hydroxypropane, or other like hydroxylated diamines or polyamines, and the like. An excess of the amine relative to the aldehyde groups of the dextran is used to insure substantially complete conversion of the aldehyde functions to Schiff base groups.

A reducing agent, such as $NaBH_4$, $NaBH_3CN$ or the like, is used to effect reductive stabilization of the resultant Schiff base intermediate. The resultant adduct can be purified by passage through a conventional sizing column to remove cross-linked dextrans.

Other conventional methods of derivatizing a dextran to introduce amine functions can also be used, e.g., reaction with cyanogen bromide, followed by reaction with a diamine.

The aminodextran is then reacted with a derivative of the particular drug, toxin, chelator, immunomodulator, boron addend, or other therapeutic agent to be loaded, in an activated form, preferably, a carboxyl-activated derivative, prepared by conventional means, e.g., using dicyclohexylcarbodiimide (DCC) or a water soluble variant thereof, to form an intermediate adduct.

Alternatively, polypeptide toxins such as pokeweed antiviral protein or ricin A-chain, and the like, can be coupled to aminodextran by glutaraldehyde condensation or by reaction of activated carboxyl groups on the protein with amines on the aminodextran.

Chelators for radiometals or magnetic resonance enhancers are well-known in the art. Typical are derivatives of ethylenediaminetetraacetic acid (EDTA) and diethylenetriaminepentaacetic acid (DTPA). These chelators typically have groups on the side chain by which the chelator can be attached to a carrier. Such groups include, e.g., benzylisothiocyanate, by which the DTPA or EDTA can be coupled to the amine group of a carrier. Alternatively, carboxyl groups or amine groups on a chelator can be coupled to a carrier by activation or prior derivatization and then coupling, all by well-known means.

Boron addends, such as carboranes, can be attached to antibody components by conventional methods. For example, carboranes can be prepared with carboxyl functions on pendant side chains, as is well known in the art. Attachment of such carboranes to a carrier, e.g., aminodextran, can be achieved by activation of the carboxyl groups of the carboranes and condensation with amines on the carrier to produce an intermediate conjugate. Such intermediate conjugates are then attached to antibody components to produce therapeutically useful immunoconjugates, as described below.

A polypeptide carrier can be used instead of aminodextran, but the polypeptide carrier must have at least 50 amino acid residues in the chain, preferably 100-5000 amino acid residues. At least some of the amino acids should be lysine residues or glutamate or aspartate residues. The pendant amines of lysine residues and pendant carboxylates of glutamine and aspartate are convenient for attaching a drug, toxin, immunomodulator, chelator, boron addend or other therapeutic agent. Examples of suitable polypeptide carriers include polylysine, polyglutamic acid, polyaspartic acid, copolymers thereof, and mixed polymers of these amino acids and others, e.g., serines, to confer desirable solubility properties on the resultant loaded carrier and immunoconjugate.

Conjugation of the intermediate conjugate with the antibody component is effected by oxidizing the carbohydrate portion of the antibody component and reacting the resulting aldehyde (and ketone) carbonyls with amine groups remaining on the carrier after loading with a drug, toxin, chelator, immunomodulator, boron addend, or other therapeutic agent. Alternatively, an intermediate conjugate can be attached to an oxidized antibody component via amine groups that have been introduced in the intermediate conjugate after loading with the therapeutic agent. Oxidation is conveniently effected either chemically, e.g., with $NaIO_4$ or other glycolytic reagent, or enzymatically, e.g., with neuraminidase and galactose oxidase. In the case of an aminodextran carrier, not all of the amines of the aminodextran are typically used for loading a therapeutic agent. The remaining amines of aminodextran condense with the oxidized antibody component to form Schiff base adducts, which are then reductively stabilized, normally with a borohydride reducing agent.

Analogous procedures are used to produce other immunoconjugates according to the invention. Loaded polypeptide

carriers preferably have free lysine residues remaining for condensation with the oxidized carbohydrate portion of an antibody component. Carboxyls on the polypeptide carrier can, if necessary, be converted to amines by, e.g., activation with DCC and reaction with an excess of a diamine.

The final immunoconjugate is purified using conventional techniques, such as sizing chromatography on Sephacryl S-300.

Alternatively, immunoconjugates can be prepared by directly conjugating an antibody component with a therapeutic agent. The general procedure is analogous to the indirect method of conjugation except that a therapeutic agent is directly attached to an oxidized antibody component.

For application to linking MHC I/II peptide/B7 molecules to a latex which has previously conjugated to biotin, for avidin assisted linking to a multifunctional ligand, it will be appreciated that biotin can be conjugated to a part of a latex sphere which is then linked to MHC peptide and B7 molecules by placing the spheres in a confluent layer or in the spheres in a microwells such that only part of the sphere is exposed for conjugation and then coating the spheres onto avidin coated plates for the B7 and MHC linkage.

It will be appreciated that other therapeutic agents can be substituted for the chelators described herein. Those of skill in the art will be able to devise conjugation schemes without undue experimentation.

As a further illustration, a therapeutic agent can be attached at the hinge region of a reduced antibody component via disulfide bond formation. For example, the tetanus toxoid peptides can be constructed with a single cysteine residue that is used to attach the peptide to an antibody component. As an alternative, such peptides can be attached to the antibody component using a heterobifunctional cross-linker, such as N-succinyl 3-(2-pyridyldithio)proprionate (SPDP). Yu et al., Int. J. Cancer 56:244 (1994). General techniques for such conjugation are well-known in the art. See, for example, Wong, CHEMISTRY OF PROTEIN CONJUGATION AND CROSS-LINKING (CRC Press 1991); Upeslacis et al., "Modification of Antibodies by Chemical Methods," in MONOCLONAL ANTIBODIES: PRINCIPLES AND APPLICATIONS, Birch et al. (eds.), pages 187-230 (Wiley-Liss, Inc. 1995); Price, "Production and Characterization of Synthetic Peptide-Derived Antibodies," in MONOCLONAL ANTIBODIES: PRODUCTION, ENGINEERING AND CLINICAL APPLICATION, Ritter et al. (eds.), pages 60-84 (Cambridge University Press 1995).

As described above, carbohydrate moieties in the Fc region of an antibody can be used to conjugate a therapeutic agent. However, the Fc region is absent if an antibody fragment is used as the antibody component of the immunoconjugate. Nevertheless, it is possible to introduce a carbohydrate moiety into the light chain variable region of an antibody or antibody fragment. See, for example, Leung et al., J. Immunol. 154:5919 (1995); Hansen et al., U.S. Pat. No. 5,443,953 (1995). The engineered carbohydrate moiety is then used to attach a therapeutic agent.

In addition, those of skill in the art will recognize numerous possible variations of the conjugation methods. For example, the carbohydrate moiety can be used to attach polyethyleneglycol in order to extend the half-life of an intact antibody, or antigen-binding fragment thereof, in blood, lymph, or other extracellular fluids. Moreover, it is possible to construct a "divalent immunoconjugate" by attaching therapeutic agents to a carbohydrate moiety and to a free sulfhydryl group. Such a free sulfhydryl group may be located in the hinge region of the antibody component.

Methods for determining the binding specificity of an antibody are well-known to those of skill in the art. General methods are provided, for example, by Mole, "Epitope Mapping," in METHODS IN MOLECULAR BIOLOGY, VOLUME 10: IMMUNOCHEMICAL PROTOCOLS, Manson (ed.), pages 105-116 (The Humana Press, Inc. 1992). More specifically, competitive blocking assays for example to determine CD22 epitope specificity are described by Stein et al., Cancer Immunol. Immunother. 37:293 (1993), and by Tedder et al., U.S. Pat. No. 5,484,892 (1996).

In another aspect the invention is directed to a bispecific ligand, preferably a bispecifc antibody, comprising at least a first ligand, preferably an antibody component, which binds specifically to a first cell surface associated ligand and at least a second ligand, preferably a second antibody component which binds specifically to a second cell surface associated ligand on the same cell, and wherein the functional affinity of at least one and preferably both of said antibody components is selected so as to substantially limit functional binding unless both of said first and second antibody components are substantially contemporaneously bound to said cell. It is known to provide bifunctional ligands wherein functional binding, for example, to accomplish signal transduction, is predicated on both ligands being bound or cross-linking. However this effect is not contemplated to be predicated on differentially controlling the functional affinity of the respective ligands. According to a broad aspect of this invention (in which inclusion of a ligand which binds to a lymphatic vessel associated marker is optional), the invention excludes known such bispecific ligands which inherently have a suitable differential functional affinity. Such bispecific ligand are mentioned herein. By controlling the affinity of at least one of said ligands, for example where the functional affinity of one said ligands is substantially less than that of the other ligand the invention contemplates that a substantially greater percentage of the administered dose of the bispecific ligand will affect cells in which only both ligands are present, and/or that a reduced percentage of the dose administered will functionally bind to the cells in virtue only of the reduced functional affinity ligand. The invention also contemplates that functional affinity of one ligand is greatly increased to establish the functional affinity differential and that the functional affinity of both ligands is reduced relative to that of a standard, for example relative to that of a comparable ligands in hand or

known in the art or identified by phage display, ribsome display or other comparable techniques using a single such ligand. The invention also contemplates that a microarray (or library) of bispecific ligands in which for example, the bispecific ligand is "tethered" (ie. immobilized) directly or indirectly in virtue of one or more amino acid residues which are positioned within the molecule to preferably minimally interfere with any binding, and in which the signal (eg its intensity) associated with a single ligand-binding interaction can be differentiated from a two or more ligand interactions, for example cell surface binding (alternatively the ligands or cell may be immobilized) and that ribsome and phage display could be adapted to bispecific single domain antibodies constituting a single chain (see references herein) by elongating the end of the chain from which the molecule is tethered. The invention contemplates that the affinity of one such ligand may be fixed and that the variability in members of the library lies in the permutations of certain key residues to which binding is attributable which can readily be identified by persons skilled in the art. The invention also contemplates assessing single ligand binding capability of successful bi-ligand binders for example by blocking the other (non-assessed at that time) ligand (eg. with correlative ligand or a mimotope thereof) and for example determining limited or non-existent such binding to as well as using inclined ligand testing surfaces for washing over the correlative ligand, for example of defined surface area, including preferably defined lengths and widths and concentrations / distributions / amounts of the bound ligand, where the degree of incline is selected to roughly simulate the micro-environment of the comparable in vivo target, be it a stationary cell with a roughly defined average shear force of bathing fluids eg. within a tumor or in the lymphatic system, or a mobile cell within a vein, artery, or lymphatic vessel, including those of different sizes. The invention is also directed to a mthod of generating a target ligand or improving the target specificity of any ligand by using a population of variants of that ligand within a micro-environment simulated microarray system in which the at least one of the follwing factors is simulated: concentration or amount or distribution of correlative ligand, shear force and shape using length and width parameters to simulates intraluminal diameter and length. The invention also contemplates in the case of a multifunctional ligand or in the case of a bispecific or multispecfic ligand (as herein described) that the affinity of its component binding ligands may be selected for venous or arterial tageting or to accommodate lymphatic system targeting or targeting within or through tissues or combinations of the aforementioned eg. median, average or or weighted compromises to improve desired targeting. In a preferred embodiment the first ligand is selected on the basis of its ability to at least partially discriminate between a target population of cells (eg. a ligand that is "associated" with a target population of cells) and a non-target population of cells (in one embodiment it is selected so as to have no other effect other than binding for targeting purposes) and the second ligand is selected for its ability to modulate the activity of the targeted cell, optionally in virtue of binding alone eg. without delivering a payload (the term modulate referring broadly to any desired effect on the cell or its functionality) In this case the functional affinity for the ligand which is targeted for modulating the activity of the cell is selected so as to reduce the likelihood of binding unless binding has first or contemporaneously occurred to the first ligand targeted for selectivity (eg. the second ligand would have monovalent as opposed to divalent binding to the ligand required for selectivity and/or from 0.20 to 10^{9} fold reduction in affinity (for example as measured by Biacore) relative to the binding affinity for the first ligand, preferably a greater than 20% reduction in affinity, preferably a greater than 20% reduction in affinity, preferably a greater than 100% reduction in affinity, preferably a greater than 200% reduction in affinity, preferably a greater than 300% reduction in affinity, preferably a greater than 400% reduction in affinity, preferably a greater than 500% reduction in affinity, preferably a greater than 600% reduction in affinity, preferably a greater than 700% reduction in affinity, preferably a greater than 800% reduction in affinity, preferably a greater than 900% reduction in affinity, preferably a greater than 1000% reduction in affinity, preferably a greater than 2000% reduction in affinity, preferably a greater than 3000% reduction in affinity, preferably a greater than 4000% reduction in affinity, preferably a greater than 5000% reduction in affinity, preferably a greater than 6000% reduction in affinity, preferably a greater than 7000% reduction in affinity, preferably a greater than 8000% reduction in affinity, preferably a greater than 9000% reduction in affinity, preferably a greater than 10000% reduction in affinity, preferably a greater than 20000% reduction in affinity, preferably a greater than 30000% reduction in affinity, preferably a greater than 40000% reduction in affinity, preferably a greater than 50000% reduction in affinity, preferably a greater than 60000% reduction in affinity, preferably a greater than 70000% reduction in affinity, preferably a greater than 80000% reduction in affinity, preferably a greater than 90000% reduction in affinity, preferably a greater than 100000% reduction in affinity , preferably a greater than 200000% reduction in affinity , preferably a greater than 300000% reduction in affinity, preferably a greater than 400000% reduction in affinity, preferably a greater than 500000% reduction in affinity preferably a greater than 600000% reduction in affinity preferably a greater than 700000% reduction in affinity preferably a greater than 800000% reduction in affinity preferably a greater than 900000% reduction in affinity, preferably a greater than 1000000% reduction in affinity, preferably a greater than 2000000% reduction in affinity preferably a greater than 3000000% reduction in affinity preferably a greater than 4000000% reduction in affinity preferably a greater than 5000000% reduction in affinity preferably a greater than 6000000% reduction in affinity preferably a greater than 7000000% reduction in affinity preferably a greater than 8000000% reduction in affinity preferably a greater than 9000000% reduction in affinity preferably a greater than 10000000% reduction in affinity preferably a greater than 20000000% reduction in affinity preferably a greater than 3000000% reduction in affinity, preferably a greater than 40,000,000% reduction in affinity, preferably a greater than 50000000% reduction in affinity, preferably a greater than 60000000% reduction in affinity, preferably a greater than 70000000% reduction in affinity, preferably a greater than 80000000% reduction in affinity, preferably a greater than 90000000% reduction in affinity preferably a greater than 100,000,000% reduction in affinity, preferably a reduction in affinity of between one and two orders of magnitude, preferably a reduction in affinity of between two and three orders of magnitude, preferably a reduction in affinity of between three and four orders of magnitude, preferably a reduction in affinity of between four and five orders of magnitude, preferably a reduction in affinity of between five and six orders of magnitude, preferably a reduction in affinity of between six and seven orders of magnitude preferably a reduction in affinity of between seven and eight orders of

magnitude, preferably a reduction in affinity of between eight and nine orders of magnitude, preferably a reduction in affinity of between nine and ten orders of magnitude. It will be appreciated that a suitable reduction in affinity, if any, will depend on the valency of the respective first and second ligands and the selected affinity of the first ligand, which for example may have been augmented. The invention also contemplates a trispecific (and triavalent) ligand in which two ligands differently define its specificity to reduce the likelihood of an undesired effect attributable to the function exerting moiety binding alone. In terms of the physical constitution of a ligand having a trispecific binding capability, the invention contemplates linking three monovalent dabs, MRUs or the like or mixed combinations thereof or two bivalent dabs, MRUs or the like or mixed combinations thereof (see WO 99/42077, US 6174691, WO0029004,Camel single-domain antibodies as modular building units in J Biol Chem. 2000 Oct 25, & Mulligan-Kehoe U.S. patents including US 5702892, US 5824520; se also US 6040136) (in the latter case optionally one or both may be bispecific and linked by well known methods in the art (see WO 99/42077, Celltech's TFM, leucine zippers, US 5,910,573, US5892020, EP 0654085B, see also EP 0318554B). The term functional binding is used to refer to binding which yields the desired effect, for example a therapeutic effect on a target cell population attributable to the binding to one or both ligands. Using the previous example, one ligand, eg. the first ligand, may be used to target activated immune cells, and the second ligand may be different and may upon being bound to, for example result in inactivation, anergy, apoptosis or reduced capacity for endothelial adhesion of the immune cell. In this case, the invention contemplates that the functional affinity of the antibody component which binds to the second ligand is selected such that binding is unlikely to occur without binding to the specificity dictating ligand, for example the ratio of targeted relative non-targeted cells affected by the dose administered is approximately 1.10 to 1, preferably approximately 1.15 to 1, more preferably approximately 1.20 to 1, more preferably approximately 1.25 to 1, more preferably approximately 1.30 to 1, more preferably approximately 1.35 to 1, more preferably approximately 1.40 to 1, more preferably approximately 1.45 to 1, more preferably approximately 1.50 to 1, more preferably approximately 1.55 to 1, more preferably approximately 1.60 to 1, more preferably approximately 1.60 to 1, more preferably approximately 1.65 to 1, more preferably approximately 1.70 to 1, more preferably approximately 1.75 to 1, more preferably approximately 1.80 to 1, more preferably approximately 1.85 to 1, more preferably approximately 1.90 to 1, more preferably approximately 1.95 to 1, more preferably approximately 2 to 1, more preferably greater than 2 to 1, more preferably approximately greater than 3 to 1, more preferably approximately greater than 4 to 1, more preferably greater than 5 to 1, more preferably greater than 6 to 1, more preferably greater than 7 to 1, more preferably greater than 8 to 1 , more preferably greater than 9 to 1 , more preferably greater than 10 to 1 , more preferably greater than 20 to 1 , more preferably greater than 30 to 1 , more preferably greater than 40 to 1 , more preferably greater than 50 to 1 , more preferably greater than 60 to 1, more preferably greater than 70 to 1, more preferably greater than 80 to 1, more preferably greater than 90 to 1, more preferably greater than 100 to 1, more preferably greater than 500 to 1 , more preferably greater than 1000 to 1, more preferably greater than 10,000 to 1, more preferably greater than 100,000 to 1, more preferably greater than 500,000 to 1 more preferably greater than 1,000,000 to 1.

It will be appreciated by persons skilled in the art that the foregoing aspects of the invention apply to a variety of different combinations of immune function or other therapeutic function exerting ligands and specificity dictating ligands including those involved in immune signaling, stimulatory, co-stimulatory, inhibitory, adhesion or other interactions, including without limitation, cytokine receptors, ligands associated with immune cell adhesion, ligands to which binding results in stimulation, activation, apoptosis, anergy or costimulation, or ligands which differentiate between different populations or subpopulations or immune cells (see eg. US 6135941, WO 00/63251, WO 00/61132, US 6120767), including sub-populations of B cells and T cells (see for example US 6197524) activated versus non-activated lympocytes, diseased or disease-causing cells versus non-diseased / disease causing lymphocytes (see for exampleWO 01/13945A1, US 6132980,) and specific immune cell clones for example those having specific Ig type and MHC-peptide type ligands / and correlative ligands. Examples of such ligands include CCR5, CTLA-4, LFA-1, LFA-3. ICAMs eg. ICAM-1, CD2, CD3, CD4 (eg see US 6,136,310), CD18, CD22, CD40, CD44; CD80, CD86, CD134 and CD154, to name only a few (see also US6087475: PF4A receptor) (see also Glennie MJ et al. Clinical Trial of Antibody Therapy. Immunology Today Aug 2000, Vol. 21 (no. 8) p.406).

The invention also contemplates that the therapeutic function or immune function effecting ligand is also a specificity imparting ligand, which in the case of for example, an antigen presenting cell may be an antibody which recognizes and binds to a specific MHC peptide complex, as is established in the art (see pertinent Chames et al. references herein, see also WO 97/02342 , Direct selection of a human antibody fragment directed against the tumor T-cell epitope HLA-A1-MAGE-A1 from a nonimmunized phage-Fab library. Proc Natl Acad Sci U S A. 2000 Jul 5; 97(14):7969-74). In this case it will be appreciated that the APC targeting ligand assist the particular MHC peptide binding antibody to bind to its target.

See also WO 97/07819 which is hereby disclaimed with respect to all relevant aspects of the invention herein insofar as inherently disclosed therein. See also US 5,770,403 with respect to antibodies which bind to cytokines.

Depending on the mode of action of the particular immunotherapeutic, functional binding may for example simply refer to a significantly reduced percentage of the total administed dose which is bound to cells that do not express both ligands and for example where internalization is part of the mode of action may refer to a significantly reduced percentage of the total administed dose which is capable of internalizing where both ligands are not present. The term "associated" is to as above to refer to a ligand which is not necessarily exclusively expressed on the target population of cells but may be expressed or over-expressed to functional (selective) advantage on a target population of cells when compared to the non-target population. Preferably said respective antibody components recognize a substantially different subset of non-targetted tissues so that functional binding to a non-targetted

tissue is substantially precluded. (It will be appreciated that this strategy can be accomplished with two different antibodies have differing and preferably non-overlapping normal ie. non-targeted tissue distributions). In a preferred embodiment the target cell is a cancer cell and the respective first and second cell surface associated ligands are expressed on different subsets of normal cells, preferably non-overlapping subsets, so as to minimize deleterious normal cell targeting and distibute the undesired effects or normal cell targeting (eg. with a toxin), to different cell populations. For example in the case of tumor cell targeting one or both ligands may be expressed exclusively on a single tumor type (eg. a human sarcoma or carcinoma, e.g., fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma; papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma; leukemias, e.g., acute lymphocytic leukemia and acute myelocytic leukemia (myeloblastic, promyelocytic, myelomonocytic, monocytic and erythroleukemia); chronic leukemia (chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia); and polycythemia vera, lymphoma (Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, and heavy chain disease) *or* a particular category of tumor types (eg. adenocarcinomas, tumors of neuroectodermal origin, *or* on multiple different tumor types or categories of tumor. One or both components (they may be the same or different) may be a dAb, a scFv, an Fab, a minibody moiety or a substantially intact antibody, for example both may be scFvs and the resulting product may be a diabody, triabody, or tetrabody. For example in a preferred embodiment the bispecific antibody comprises two dAb components comprising linked via a linker (see above) and having at least at least part of a constant region for fusion for example to a toxin (eg. at least a partial hinge region, and preferably also at least a partial CH2 domain (optionally also at least a partial CH3 domain). In another embodiment, a trispecific antibody or tetraspecific antibody with at least two different and preferably 3 or 4 subsets (preferably at least one or more of such subsets being non-overlapping subsets) of non-targeted cell reactivities may be employed in the form of a trispecific or tetraspecific antibody respectively whereby up to three or four different pairs of ligands are targeted, so as further minimize normal cell targeting and also preferably target a heterogenous population of cells within the same tumor. Ligands with distributions on normal tissues are well known, some being referenced herein, for example CEA, CD-20, P53, epidermal growth factor, including known multicarcinomic and pancarcinomic ligands (eg. see US 5, 171,665, US 4349528.The term functional binding is used to mean binding for the purpose of accomplishing the object of the binding, for example binding in a sufficient degree (% of the dose) and for a sufficient duration to inhibit or enhance a particular effect, such as cell killing, for example in the case where one both antibody components are selected for their ability to internalize, binding for a sufficient duration to permit internalization, for example to deliver a toxic payload. As discussed above, the term substantially is used to refer to a degree which provides a significant benefit from a therapeutic standpoint. Examples of tumor associated antigens (eg. WO 01/21828) and targets and related antibodies are referenced throughout the disclosure and the foregoing aspect of the invention is for greater certainty directed to bispecific antibodies (including trispecific and tetraspecific antibodies, optionally including a component which also binds to a lymphatic vessel associated ligand); which target each of the combinations and permuations of the target cell (diseased, disease causing or immune) associated antigens, ligands, epitopes or receptors well known to those skilled in the art, herein directly or indirectly referenced or referenced in the materials herein incorporated by reference (ie. permutations and combinations of pairs or where a tri-or tetra- specific antibody is used possibly permutations of (3 or 4) groups of pairs including for example pairs in which one member is used for targeting and the second is used for modulation puposes such modulation including without limitation, simple binding eg. to deliver a payload, apoptosis inducing (eg. anti-fas), modified vascular adhesion properties (eg. anti-CD44), modified cytokine binding (anti-CCR5) etc.(for relevant ligands/markers see also USP 6,010,902 and the references cited therein, Samter's Immunologic Diseases, Fifth and Sixth Edition, Lippincott, Frank Austen, MD Michael M. Frank, MD John P. Atkinson, MD Harvey I. Cantor, MD (6th-ISBN: 0-7817-2120-2); Fundamental Virology, Third and Fourth Edition, Lippincott David M. Knipe, PhD Peter M. Howley, MD, Diane E. Griffin, MD, PhD Robert A. Lamb, PhD, ScD Malcolm A. Martin, MD Bernard Roizman, ScD Stephen E. Straus, MD (4th-ISBN: 0-7817-1833-3); Arthritis and Allied Conditions - A Textbook of Rheumatology, Thirteenth and Fourteenth Editions, William J. Koopman, MD 14th:ISBN: 0-7817-2240-3, November 2000; Cancer - Principles and Practice of Oncology, Fifth and Sixth Editions, Lippincott, Vincent T. DeVita, Jr., MD Samuel Hellman, MD Steven A. Rosenberg, MD, PhD ISBN: 0-7817-2229-2; Dubois' Lupus Erythematosus, Fifth Edition, Daniel J. Wallace, MD ISBN: 0-683-08665-0, December 1996; Cytokine Therapeutics in Infectious Diseases, Steven M. Holland, MD, PhD, Lippincott, ISBN: 0-7817-1625-X, US 6054561), in each of their permuatations of size/valency (ie. dabs, scFv, diabodies etc herein referenced) as applied to each of the applicable disease conditions herein referenced or otherwise known to those skilled in the art.

With respect to recombinant techniques for producing Fv fragments see also WO 88/01649, WO 88/06630, WO 88/07085, WO 88/07086, and WO 88/09344.

With respect to preparing ligands for specific MHC peptide complexes see also WO 01/22083; Direct selection of a human antibody fragment directed against the tumor T-cell epitope HLA-A1-MAGE-A1 from a nonimmunized phage-Fab library. Proc Natl Acad Sci U S A. 2000 Jul 5;97(14):7969-74.

With respect to bispecific antigen binding constructs that are suitable for for binding to more than one antigen on the same cell see also Schmiedl A et al. Protein Eng 2000 Oct 13(10):725-34.

Preferred immunoconjugates include radiolabeled antibody components and conjugates of an anti-Lyve-1 antibody component and an antbody component which comprises an immunomodulator.

A radiolabeled immunoconjugate may comprise an .alpha.-emitting radioisotope, a .B-emitting radioisotope, a gamma emitting radioisotope, an Auger electron emitter, a neutron capturing agent that emits alpha-particles or a radioisotope that decays by electron capture. Suitable radioisotopes include ^{198} Au, ^{32} p,. ^{125} I, ^{131} I, ^{90} Y, ^{186} Re, ^{188} Re, ^{67} Cu, ^{211} At, and the like.

As discussed above, a radioisotope can be attached to an antibody component directly or indirectly, via a chelating agent. For example, ^{67} Cu, considered one of the more promising radioisotopes for radioimmunotherapy due to its 61.5 hour half-life and abundant supply of beta particles and gamma rays, can be conjugated to an antibody component using the chelating agent, p-bromoacetamido-benzyl-tetraethylaminetetraacetic acid (TETA) . Chase, "Medical Applications of Radioisotopes," in Remington's Pharmaceutical Sciences, 18th Edition, Gennaro et al. (eds.), pages 624-652 (Mack Publishing Co. 1990) (see also 19th edition of Reminton's). Alternatively, ^{90} Y, which emits an energetic beta particle, can be coupled to an antibody component using diethylenetriaminepentaacetic acid (DTPA). Moreover, a method for the direct radiolabeling of the antibody component with ^{131} I is described by Stein et al., Antibody Immunocon). Radiopharm. 4: 703 (1991) (see also USP 6, 080, 384).

Alternatively, boron addends such as carboranes can be attached to antibody components, as discussed above.

In addition, therapeutic immunoconjugates can comprise an immunomodulator moiety suitable for application for the purposes herein. Broadly speaking, the term "immunomodulator" includes cytokines, stem cell growth factors, lymphotoxins, such as tumor necrosis factor (TNF), and hematopoietic factors, such as interleukins (e.g., interleukin-1 (IL-1), IL-2, IL-3, IL6, IL-10 and IL-12), colony stimulating factors (e.g., granulocyte-colony stimulating factor (G-CSF) and granulocyte macrophage-colony stimulating factor (GM-CSF)), interferons (e.g., interferonsalpha, -beta and gamma.), the stem cell growth factor designated "S1 factor," erythropoietin and thrombopoietin. Examples of suitable immunomodulator moieties include IL-2, IL-6, IL-10, IL12, interferon-gamma., TNF-alpha., and the like.

A related form of therapeutic protein is a fusion protein comprising an antibody moiety and an immunomodulator moiety.

Methods of making antibody-immunomodulator fusion proteins are known to those of skill in the art as discussed herein. For example, antibody fusion proteins comprising an interleukin-2 moiety are described by Boleti et al., Ann. Oncol. 6:945 (1995), Nicolet et al., Cancer Gene Ther. 2:161 (1995), Becker et al., Proc. Nat'l Acad. Sci. USA 93:7826 (1996), Hank et al., Clin. Cancer Res. 2:1951 (1996), and Hu et al., Cancer Res. 56:4998 (1996). In addition, Yang et al., Hum. Antibodies Hybridomas 6:129 (1995), describe a fusion protein that includes an F(ab')$_2$ fragment and a tumor necrosis factor alpha moiety.

Such immunoconjugates and antibody-immunomodulator fusion proteins provide a means to deliver an immunomodulator to a target cell and are particularly useful against tumor cells. The cytotoxic effects of immunomodulators are well known to those of skill in the art. See, for example, Kle et al., "Lymphokines and Monokines," in Biotechnology and Pharmacy, Pessuto et al. (eds.), pages 53-70 (Chapman & Hall 1993) as well as other references herein cited. As an illustration, interferons can inhibit cell proliferation by inducing increased expression of class I histocompatibility antigens on the surface of various cells and thus, enhance the rate of destruction of cells by cytotoxic T lymphocytes. Furthermore, tumor necrosis factors, such as TNF-alpha., are believed to produce cytotoxic effects by inducing DNA fragmentation.

Moreover, therapeutically useful immunoconjugates can be prepared in which an antibody component is conjugated to a toxin or a chemotherapeutic drug. Illustrative of toxins which are suitably employed in the preparation of such conjugates are ricin, abrin, ribonuclease, DNase I, Staphylococcal enterotoxin-A, pokeweed antiviral protein, gelonin, diphtherin toxin, Pseudomonas exotoxin, and Pseudomonas endotoxin. See,references herein as well as for example, Pastan et al., Cell 47:641 (1986), and Goldenberg, CA-A Cancer Journal for Clinicians 44:43 (1994). Other suitable toxins are known to those of skill in the art.

With to respect to bispecific antibody constructs which are capable of binding simultaneously to two ligands on the same cell see also WO96/32841. Various such constructs are known in the art.

An alternative approach to introducing the combination of therapeutic antibody and toxin is provided by antibody-toxin fusion proteins. An antibody-toxin fusion protein is a fusion protein that comprises an antibody moiety and a toxin moiety. Methods for making antibody-toxin fusion proteins are known to those of skill in the art (see references cited herein); antibody-Pseudomonas exotoxin A fusion proteins have been described by Chaudhary et al., Nature 339:394 (1989), Brinkmann et al., Proc. Nat'l Acad. Sci. USA 88:8616 (1991), Batra et al., Proc. Nat'l Acad. Sci. USA 89:5867 (1992), Friedman et al., J. Immunol. 150:3054 (1993), Wels et al., Int. J. Can. 60:137

(1995), Fominaya et al., J. Biol. Chem. 271:10560 (1996), Kuan et al., Biochemistry 35:2872 (1996), and Schmidt et al., Int. J. Can. 65:538 (1996). Antibody-toxin fusion proteins containing a diphtheria toxin moiety have been described by Kreitman et al., Leukemia 7:553 (1993), Nicholls et al., J. Biol. Chem. 268:5302 (1993), Thompson et al., J. Biol. Chem. 270:28037 (1995), and Vallera et al., Blood 88:2342 (1996). Deonarain et al., Tumor Targeting 1:177 (1995), have described an antibody-toxin fusion protein having an RNase moiety, while Linardou et al., Cell Biophys. 24-25:243 (1994), produced an antibody-toxin fusion protein comprising a DNase I component. Gelonin was used as the toxin moiety in the antibody-toxin fusion protein of Wang et al., Abstracts of the 209th ACS National Meeting, Anaheim, Calif., Apr. 2-6, 1995, Part 1, BIOT005. As a further example, Dohlsten et al., Proc. Nat'l Acad. Sci. USA 91:8945 (1994), reported an antibody-toxin fusion protein comprising Staphylococcal enterotoxin-A. Numerous other examples have been reported in the literature.

Useful cancer chemotherapeutic drugs for the preparation of immunoconjugates include nitrogen mustards, alkyl sulfonates, nitrosoureas, triazenes, folic acid analogs, pyrimidine analogs, purine analogs, antibiotics, epipodophyllotoxins, platinum coordination complexes, hormones, and the like. Suitable chemotherapeutic agents are described in Remington's Pharmaceutical Sciences, 19th Ed. (Mack Publishing Co. 1995), and in Goodman and Gilman's The Pharmacological Basis of Therapeutics, 7th Ed. (MacMillan Publishing Co. 1985). Other suitable chemotherapeutic agents, such as experimental drugs, are known to those of skill in the art.

In addition, therapeutically useful immunoconjugates can be obtained by conjugating photoactive agents or dyes to an antibody composite. Fluorescent and other chromogens, or dyes, such as porphyrins sensitive to visible light, have been used to detect and to treat lesions by directing the suitable light to the lesion. In therapy, this has been termed photoradiation, phototherapy, or photodynamic therapy (Jori et al. (eds.), Photodynamic Therapy of Tumors and Other Diseases (Libreria Progetto 1985); van den Bergh, Chem. Britain 22:430 (1986)). Moreover, monoclonal antibodies have been coupled with photoactivated dyes for achieving phototherapy. Mew et al., J. Immunol. 130:1473 (1983); idem., Cancer Res. 45:4380 (1985); Oseroff et al., Proc. Natl. Acad. Sci. USA 83:8744 (1986); idem., Photochem. Photobiol. 46:83 (1987); Hasan et al., Prog. Clin. Biol. Res. 288:471 (1989); Tatsuta et al., Lasers Surg. Med. 9:422 (1989); Pelegrin et al., Cancer 67:2529 (1991). However, these earlier studies did not include use of endoscopic therapy applications, especially with the use of antibody fragments or subfragments. Thus, the present invention contemplates the therapeutic use of immunoconjugates comprising photoactive agents or dyes.

With respect to a multifunctional ligand having a first portion that binds to both lymphatic endothelial cells and tumor vasculature, the invention contemplates using phage display or ribosome display to generate an antibody that binds to vefgr-3 as well as one or both of of vegfr-2 or vegfr-1, having regard to the sequences of those respective receptors (see USPs 5,776,755, 5877020, 5952199, 6107046, 6130071, 6221839, 6235713, 6245530; see also WO 00/21560, WO 95/33772, WO 97/05250, WO 98/33917). Preferably the antibody does not internalize, particularly in the case where the multifunctional ligand is fused or conjugated to a toxic moiety. The invention also contemplates, for example, fusing the binding domain of VEGF-C or VEGF-D to antitumor antibody. The invention also contemplates that the risk of retargeting cancer cells to non-tumor sites of angiogenesis, can be minimized by employing one or more of the following strategies pre- and/or co-treatment with inhibitors of angiogenesis, providing the multifunctional ligand with an effector function, such as a toxic moiety, cytokine or antibody component which retargets immune cells capable of killing such cancer cells. The invention also contemplates using in combination or alone a multifunctional ligand having a second portion that comprises an anti-VEGF antibody portion which binds to one or more of the VEGF family of ligands in order to inhibit lymphangiogenesis and/or angiogenesis. (see also for example, WO 00/37025, WO 98/33917, USP 6130071, WO 01/12669). With respect to angiogenesis and particularly lymphangiogenesis see also:1: Shibuya M.Structure and function of VEGF/VEGF-receptor system involved in angiogenesis.Cell Struct Funct. 2001 Feb;26(1):25-35.2: Yonemura Y, Fushida S, Bando E, Kinoshita K, Miwa K, Endo Y, Sugiyama K,Partanen T, Yamamoto H, Sasaki T.Lymphangiogenesis and the vascular endothelial growth factor receptor (VEGFR)-3in gastric cancer.Eur J Cancer. 2001 May;37(7):918-23.3: Iljin K, Karkkainen MJ, Lawrence EC, Kimak MA, Uutela M, Taipale J, PajusolaK, Alhonen L, Halmekyto M, Finegold DN, Ferrell RE, Alitalo K.VEGFR3 gene structure, regulatory region, and sequence polymorphisms.FASEB J. 2001 Apr;15(6):1028-36.4: Tang RF, Itakura J, Aikawa T, Matsuda K, Fujii H, Koro M, Matsumoto Y.Overexpression of lymphangiogenic growth factor VEGF-C in human pancreaticcancer.Pancreas. 2001 Apr;22(3):285-92.5: Kadambi A, Carreira CM, Yun CO, Padera TP, Dolmans DE, Carmeliet P, FukumuraD, Jain RK.Vascular endothelial growth factor (VEGF)-C differentially affects tumorvascular function and leukocyte recruitment: role of VEGF-receptor 2 and hostVEGF-A.Cancer Res. 2001 Mar 15;61(6):2404-8.6: Karpanen T, Egeblad M, Karkkainen MJ, Kubo H, Ylä-Herttuala S, Jaattela M,Alitalo K.Vascular endothelial growth factor C promotes tumor lymphangiogenesis andintralymphatic tumor growth.Cancer Res. 2001 Mar 1;61(5):1786-90.7: Baldwin ME, Catimel B, Nice EC, Roufail S, Hall NE, Stenvers KL, KarkkainenMJ, Alitalo K, Stacker SA, Achen MG.The Specificity of Receptor Binding by Vascular Endothelial Growth Factor-D IsDifferent in Mouse and Man.J Biol Chem. 2001 Jun 1;276(22):19166-19171.8: Niki T, Iba S, Yamada T, Matsuno Y, Enholm B, Hirohashi S,Expression of vascular endothelial growth factor receptor 3 in blood andlymphatic vessels of lung adenocarcinoma.J Pathol. 2001 Apr;193(4):450-7.9: Veikkola T, Jussila L, Makinen T, Karpanen T, Jeltsch M, Petrova TV, Kubo H,Thurston G, McDonald DM, Achen MG, Stacker SA, Alitalo K.Signalling via vascular endothelial growth factor receptor-3 is sufficient forlymphangiogenesis in transgenic mice.EMBO J. 2001 Mar 15;20(6):1223-31.10: Koshida K, Konaka H, Kato H, Miyagi T, Egawa M, Uchibayashi T, Namiki M.[Correlation between expression of metastasis-related genes and lymph nodemetastasis in testicular cancer].Hinyokika Kiyo. 2000 Oct;46(10):775-81. Japanese.11: Achen MG, Williams RA, Minekus MP, Thornton GE, Stenvers K, Rogers PA,Lederman F, Roufail S, Stacker SA.Localization of vascular endothelial growth factor-D in malignant melanomasuggests a role in tumour

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Multimodal therapies are also contemplated within the present invention, including particularly for cancer, therapies which can be determined to be useful complementary therapies for the anti-metastatic embodiments of this invention such as anti-angiogenic Ab conjugates

In another form of multimodal therapy, subjects receive the multifunctional ligands of the present inventionand standard cancer chemotherapy. For example, "CVB" (1.5 g/m.sup.2 cyclophosphamide, 200-400 mg/m^2 etoposide, and 150-200 mg/m^2 carmustine) is a regimen used to treat non-Hodgkin's lymphoma. Patti et al., Eur. J. Haematol. 51:18 (1993). Other suitable combination chemotherapeutic regimens are well-known to those of skill in the art. See, for example, Freedman et al., "Non-Hodgkin's Lymphomas," in Cancer Medicine, Volume 2, 3rd Edition, Holland et al. (eds.), pages 2028-2068 (Lea & Febiger 1993). As an illustration, first generation chemotherapeutic regimens for treatment of intermediate-grade non-Hodgkin's lymphoma include C-MOPP (cyclophosphamide, vincristine, procarbazine and prednisone) and CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone). A useful second generation chemotherapeutic regimen is m-BACOD (methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, dexamethasone and leucovorin), while a suitable third generation regimen is MACOP-B (methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin and leucovorin). Additional useful drugs include phenyl butyrate and brostatin-1.

In general, the dosage of administered multifunctional ligands, immunoconjugates, and fusion proteins will vary depending upon such factors as the patient's age, weight, height, sex, general medical condition and previous medical history. Typically, it is desirable to provide the recipient with a dosage of antibody component, immunoconjugate or fusion protein which is generally at least in the range of from about 1 pg/kg to 10 mg/kg (amount of agent/body weight of patient), although a lower or higher dosage also may be administered as circumstances dictate, particularly to take advantage of the depot effect of the invention.

Administration of the invention including, immunoconjugates or fusion proteins to a patient can be intravenous, intraarterial, intraperitoneal, intramuscular, subcutaneous, intrapleural, intrathecal, by perfusion through a regional catheter, or by direct intralesional injection. When administering therapeutic proteins by injection, the administration may be by continuous infusion or by single or multiple boluses.

Those of skill in the art are aware that intravenous injection provides a useful mode of administration due to the thoroughness of the circulation in rapidly distributing antibodies. Intravenous administration, however, is subject to limitation by a vascular barrier comprising endothelial cells of the vasculature and the subendothelial matrix. Still, the vascular barrier is a more notable problem for the uptake of therapeutic antibodies by solid tumors. Lymphomas have relatively high blood flow rates, contributing to effective antibody delivery. Intralymphatic routes of

administration, such as subcutaneous or intramuscular injection, or by catherization of lymphatic vessels, also provide a useful means of treating lymphomas.

For example, the multifunctional ligand of the invention can optionally be administered at low protein doses, such as 20 to 100 milligrams protein per dose, given once, or repeatedly, parenterally. Alternatively, this multifunctional ligand is administered in doses of 30 to 90 milligrams protein per dose, or 40 to 80 milligrams protein per dose, or 50 to 70 milligrams protein per dose.

With regard to "low doses" of ^{131}I-labeled immunoconjugates, the invention includes a dosage is in the range of 15 to 40 mCi, 20 to 30 mCi. In contrast, a preferred dosage of ^{90}Y-labeled immunoconjugates is in the range from 10 to 30 mCi, while the more preferable range is 10 to 20 mCi.

Immunoconjugates having a boron addend-loaded carrier for thermal neutron activation therapy will normally be effected in similar ways. However, it will be advantageous to wait until non-targeted immunoconjugate clears before neutron irradiation is performed. Clearance can be accelerated using an antibody that binds to the immunoconjugate. See U.S. Pat. No. 4,624,846 for a description of this general principle.

The immunoconjugates, and fusion proteins of the present invention can be formulated according to known methods to prepare pharmaceutically useful compositions, whereby the therapeutic proteins are combined in a mixture with a pharmaceutically acceptable carrier. A composition is said to be a "pharmaceutically acceptable carrier" if its administration can be tolerated by a recipient patient. Sterile phosphate-buffered saline is one example of a pharmaceutically acceptable carrier. Other suitable carriers are well-known to those in the art. See, for example, REMINGTON'S PHARMACEUTICAL SCIENCES, 19th Ed. (1995).

For purposes of therapy, antibody components (or immunoconjugates/fusion proteins) and a pharmaceutically acceptable carrier are administered to a patient in a therapeutically effective amount. A combination of an antibody component, optionally with an immunoconjugate/fusion protein, and a pharmaceutically acceptable carrier is said to be administered in a "therapeutically effective amount" if the amount administered is physiologically significant. An agent is physiologically significant if its presence results in a detectable change in the physiology of a recipient patient. In one aspect, an agent is physiologically significant if its presence results in the inhibition of the growth of target tumor cells.

Yet another therapeutic method included in the invention is a method of treating cancer by administering to an animal suffering from cancer a pharmaceutically effective amount of one or more multifunctional ligands capable of binding to cancer cells, wherein the compound is associated with a substance capable of damaging cancer cells.

Pharmaceutical compositions herein described or alluded to include multifunctional ligands of the invention or therapeutics used in combination therapy which may be administered by a variety of routes of adminstration.

By administration of an "effective amount" is intended an amount of the compound that is sufficient to enhance or inhibit a response, is some embodiments particularly an immune response or cellular response to a multifunctional ligand. One of ordinary skill will appreciate that effective amounts of a multifunctional ligand can be determined empirically and may be employed in pure form or, where such forms exist, in pharmaceutically acceptable salt, ester or prodrug form. The multifunctional ligand may be administered in compositions in combination with one or more pharmaceutically acceptable excipients. It will be understood that, when administered to a human patient, the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgement. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the type and degree of the cellular response to be achieved; activity of the specific multifunctional ligand employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the agonist or antagonist; the duration of the treatment; drugs used in combination or coincidental with the specific agonist or antagonist; and like factors well known in the medical arts.

On administration parenterally, for example by i.v. drip or infusion, dosages optionally at leasr on the order of from 0.01 to 5 mg/kg/day; optionally 0.05 to 1.0 mg/kg/day and more preferably 0.1 to 1.0 mg/kg/day can be used. Suitable daily dosages for patients are thus on the order of from 2.5 to 500 mg p.o., optionally 5 to 250 mg p.o., optionally 5 to 100 mg p.o., or on the order of from 0.5 to 250 mg i.v., optionally 2.5 to 125 mg i.v. and optionally 2.5 to 50 mg i.v.

Dosaging may also be arranged in a patient specific manner to provide a predetermined concentration of an agonist or antagonist in the blood, as determined by the RIA technique. Thus patient dosaging may be adjusted to achieve regular on-going trough blood levels, as measured by RIA, optionally on the order of at least from 50 to 1000 ng/ml, preferably 150 to 500 ng/ml.

From above, pharmaceutical compositions are provided comprising an agonist or antagonist and a pharmaceutically acceptable carrier or excipient, which may be administered orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, drops or transdermal patch), bucally, or as an oral or nasal spray. By "pharmaceutically acceptable carrier" is meant a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The term "parenteral" as used herein refers to

modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

Optionally a composition for for parenteral injection can comprise pharmaceutically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), carboxymethylcellulose and suitable mixtures thereof, vegetable oils (such as olive oil), and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

Some compositions herein described may also contain adjuvants such as preservatives, wetting agents, emulsifying agents, and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents such as sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

In some cases, in order to prolong the effect of one or therapeutic components herein described, it is desirable to slow the absorption from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium just prior to use.

The multifunctional ligand can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to the agonist or antagonist, stabilizers, preservatives, excipients, and the like. The preferred lipids are the phospholipids and the phosphatidyl choaes (lecithins), both natural and synthetic. Methods to form liposomes are known in the art. See, for example, Prescott, Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N.Y. (1976), p. 33 et seq.

The present invention also contemplates a method of treatment in which immunomodulators are administered to prevent, mitigate or reverse radiation-induced or drug-induced toxicity of normal cells, and especially hematopoietic cells. Adjunct immunomodulator therapy allows the administration of higher doses of cytotoxic agents due to increased tolerance of the recipient mammal. Moreover, adjunct immunomodulator therapy can prevent, palliate, or reverse dose-limiting marrow toxicity. Examples of suitable immunomodulators for adjunct therapy include G-CSF, GM-CSF, thrombopoietin, IL-1, IL-3, IL-12, and the like. The method of adjunct immunomodulator therapy is disclosed by Goldenberg, U.S. Pat. No. 5,120,525.

For example, recombinant IL-2 may be administered intravenously as a bolus at 6 x 10^5 IU/kg or as a continuous infusion at a dose of 18 x 10^6 IU/m^2 /d. Weiss et al., J. Clin. Oncol. 10:275 (1992). Alternatively, recombinant IL-2 may be administered subcutaneously at a dose of 12 x 10^6 IU. Vogelzang et al., J. Clin. Oncol. 11:1809 (1993). Moreover, INF-.gamma. may be administered subcutaneously at a dose of 1.5 x10^6 U. Lienard et al., J. Clin. Oncol. 10:52 (1992). Furthermore, Nadeau et al., J. Pharmacol. Exp. Ther. 274:78 (1995), have shown that a single intravenous dose of recombinant IL-12 (42.5 .mu.g/kilogram) elevated IFN-.gamma. levels in rhesus monkeys.

Suitable IL-2 formulations include PROLEUKIN (Chiron Corp./Cetus Oncology Corp.; Emeryville, Calif.) and TECELEUKIN (Hoffmann-La Roche, Inc.; Nutley, N.J.). ACTIMMUNE (Genentech, Inc.; South San Francisco, Calif.) is a suitable INF-.gamma. preparation.

In the preceding detailed description, reference was made to various methodologies known to those of skill in the art of molecular biology and immunology. Publications and other materials setting forth such known methodologies to which reference was made or is made below are incorporated herein by reference in their entireties along with references cited therein as though set forth in full.

Standard reference works setting forth the general principles of recombinant DNA technology include Watson, J. D. et al, Molecular Biology of the Gene, Volumes I and II, the Benjamin/Cummings Publishing Company, Inc., publisher, Menlo Park, Calif. (1987), Darnell, J. E. et al., Molecular Cell Biology, Scientific American Books, Inc., Publisher, New York, N.Y. (1986); Lewin, B. M. Genes II, John Wiley & Sons, publishers, New York, N.Y. (1985); Old, R. W., et al., Principles of Gene Manipulation: An Introduction to Genetic Engineering, 2d edition, University of California Press, publisher, Berkeley, Calif. (1981); Maniatis, T., et al., Molecular Cloning: A Laboratory Manual, 2nd Ed. Cold Spring Harbor Laboratory, publisher, Cold Spring Harbor, N.Y. (1989), and Current Protocols in Molecular Biology, Ausubel et al., Wiley Press, New York, N.Y. (1989). Standard reference works setting forth general principles and techniques of immunology include Handbook of Experimental Immunology Blackwell Science, Incorporated, ISBN:0632009756; Antibody Engineering Blackwell Science, Incorporated, ISBN:0632009756; Encyclopedia of Immunology Therapeutic Immunology ISBN: 086542375X Blackwell Science, Incorporated ; Immunology Mosby, Incorporated, ISBN:0723429189; (1998) Morgan Kaufmann Publishers, ISBN:0122267656; Immunology 4th Ed. 2000 ISBN 0721650023; Breitling F. et al. Recombinant Abbas AK. et al. Cellular & Molecular Immunology Antibodies 1999 ISBN 0-471-17847-0; Masseyeff R. et al. Methods of Immunological Analysis Wiley-VCH ISBN 3-527-27906-7, 1992; Mountain et al. Eds, Biotechnology 2nd ed. Vol 5A 1998 ISBN 3-527-28315-3 Wiley-VCH; Campbell, A. , "Monoclonal Antibody Technology," In, Burdon, R., et al., eds, Laboratory Techniques In Biochemistry and Molecular Biology, Volume 13, Elsevier, Publisher, Amsterdam (1984);

Although the foregoing refers to particular preferred embodiments, it will be understood that the present invention is not so limited. It will occur to those of ordinary skill in the art that various modifications may be made to the disclosed embodiments and that such modifications are intended to be within the scope of the present invention.

All publications referred to herein are indicative of the level of skill of those in the art to which the invention pertains. All publications are herein (as well as references cited therein)are incorporated by reference to the same extent as if each individual publications were specifically and individdually indicated to be incorporated by reference in its entirety.

The present invention, thus generally described, will be understood more readily by reference to the preceding and following examples, which are provided by way of illustration and are not intended to be limiting of the present invention.

With respect to applications of bispecific antibodies see also *Methods Mol Biol* 2001; 166:177-92; USP 6,071,517; USP 5,897,861; USP 6,096,311; USP 5,922,845, Journal of Immunological Methods February 2001 Vol. 248(1-2) page 1-200; Mol Immunol 1999 May; 36(7):433-45; Isolation and characterization of an anti-CD16 single-chain Fv fragment and construction of an anti-HER2/neu/anti-CD16 bispecific scFv that triggers CD16-dependent tumor cytolysis.US06051227 Blockade of T lymphocyte down-regulation associated with CTLA-4 signaling; US06143297 Methods of promoting immunopotentiation and preparing antibodies with anti-CD3 antibodies; US05977318 CTLA4 receptor and uses thereof; US05968510 CTLA4 receptor and uses thereof; US05885796 CTLA4 receptor and uses thereof; US05885579 CTLA4 receptor and uses thereof; US05869050 Methods of blocking T-cell activation using anti-B7 monoclonal antibodies; US05851795 Soluble CTLA4 molecules and uses thereof; US05747034 Methods and materials for the induction of T cell anergy; US06113901 Methods of stimulating or enhancing the immune system with anti-CD3 antibodies; US05877021 B7-1 targeted ribozymes; US05844095 CTLA4 Ig fusion proteins; US06090914 CTLA4/CD28Ig hybrid fusion proteins and uses thereof; US05786152 Methods of inhibiting syp binding to a CTLA-4 receptor; US05773253 MYPPPY variants of CTL A4 and uses thereof; US05718883 Transgenic animal model for autoimmune diseases; US06045802 Enhanced immune response to an antigen by a composition of a recombinant virus expressing the antigen with a recombinant virus expressing an immunostimulatory molecule; US05811097 Blockade of lymphocyte down-regulation associated with CTLA-4 signaling; US05770197 Methods for regulating the immune response using B7 binding molecules and IL4-binding molecules; US06084067 CTLA4/CD28 ligands and uses therefor; EP01073741A2 FELINE CD80, FELINE CD86, FELINE CD28, AND FELINE CTLA-4 NUCLEIC ACID AND POLYPEPTIDES; US06130316 Fusion proteins of novel CTLA4/CD28 ligands and therefor; US06107056 SCTLA-4 gene and product; US06068984 Antibodies to lymphocyte activation antigens uses therefor;
US05861310 Tumor cells modified to express B7-2 with increased immunogenicity and uses therefor; EP00865293A1 BLOCKADE OF T LYMPHOCYTE DOWN-REGULATION ASSOCIATED WITH CTLA-4 SIGNALING; US05766570 Lymphocyte activation antigens and thereto; US05710262 Nucleic acid encoding HB15 polypeptides; US05434131 Chimeric CTLA4 receptor and methods for its use; US05316920 Lymphocyte activation antigen HB15, a member of the immunoglobulin superfamily; EP01073759A1 RECOMBINANT VIRUS EXPRESSING FOREIGN DNA ENCODING FELINE CD80, FELINE CD28, FELINE CTLA-4 OR FELINE CD86 AND USES THEREOF; US06111090 Mammalian cell surface antigens; US06083751 Chimeric receptors for the generation of selectively-activatable TH-independent cytotoxic T cells;
US05977303 Mammalian cell surface antigens; US05738852 Methods of enhancing antigen-specific T cell responses US05714667 Mice lacking expression of CTLA-4 receptor;
Bruhl H, Cihak J, Stangassinger M, Schlondorff D, Mack M. Depletion of CCR5-Expressing Cells with Bispecific Antibodies and Chemokine Toxins: A New Strategy in the Treatment of Chronic Inflammatory Diseases and HIV. J Immunol. 2001 Feb 15; 166(4):2420-2426; Tesch H, Engert A, Manzke O, Diehl V, Bohlen H.Treatment of

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With respect to pertinent diseased cells, disease causing cells and other suitable targets for bispecific antibodies, as well as optional cytokines / toxins and methods of making and using immunotoxins and related technologies including combination therapies see references herein incorporated by reference.

With respect to anti-CCR5 antibodies used to kill CCR5-expressing cells, with for example, bi-specific antibody chemokine fusions see Bruhl H. et al. J Immunol. 2001 Feb 15 166(4): 2420-2426.

With respect to targeting IKAP proteins see for example US 6172195.

With respect to pertinent diseased cells, disease causing cells and other suitable targets for immunotoxins, as well as optional toxins and methods of making and using immunotoxins and related technologies see for example US05980895 Immunotoxin containing a disulfide-stabilized antibody fragment joined to a Pseudomonas exotoxin that does not require proteolytic activation; US05686072 Epitope-specific monoclonal antibodies and immunotoxins and uses thereof; US04956453 Antihuman ovarian cancer immunotoxins and methods of thereof; US06146631 Immunotoxins comprising ribosome-inactivating proteins; US05756699 Immunotoxins comprising ribosome-inactivating Proteins; US05744580 Immunotoxins comprising ribosome-inactivating Proteins; US05837491 Polynucleotides encoding gelonin sequences; US06146850 Proteins encoding gelonin sequences; US05185434 US05578706 Methods and compositions concerning homogenous immunotoxin preparations; US05980896 Methods and compositions containing a glycopeptide constituent which inactivates ribosomes, modified on its Prolonged-action immunotoxins containing a glycopeptide constituent which inactivates ribosomes, modified on its polysaccharide units; US04958009 Anti-human ovarian cancer immunotoxins and methods of use thereof; US05980896 Antibodies reactive with human carcinomas; US06074644 Nucleic acids encoding immunotoxins containing a disulfide-stabilized antibody fragment replacing half or more of domain IB of pseudomonas exotoxin, and methods of use of the encoded immunotoxins; US05942230 Composition of immunotoxins and retinoids and use thereof; US05059413 Scintigraphic monitoring of immunotoxins using radionuclides and heterobifunctional chelators; US04919928 Conjugates in which a monovalent carboxylic ionophore is associated by means of a covalent bond with a macromolecule, their use as immunotoxin potentiators and the intermediate activated ionophores; US04911912 Ribosome-inactivating glycoproteins, modified by oxidation of their osidic units and reduction, and in vivo prolonged-action immunotoxins containing such a glycoprotein; US04911911 Ribosome-inactivating glycoproteins, modified by oxidation of their osidic units and formation of a schiff's base and in-vivo prolonged action immunotoxins containing such a glycoprotein; US05876438 Polymeric device for the delivery of immunotoxins for the prevention of secondary cataract; US05165923 Methods and compositions for

the treatment of Hodgkin's disease; US04888415 2/19/1989 Gelonin immunotoxin; US04749566 Pharmaceutical composition comprising a combination of at least one immunotoxin and at least one mannose-containing polymer; US04714759 Immunotoxin therapy of allergy; WO00041474A2 ANTI-CD3 IMMUNOTOXINS AND THERAPEUTIC USES THEREFOR; US05869045 Antibody conjugates reactive with human carcinomas; US05562907 Method to prevent side-effects and insensitivity to the therapeutic uses of toxins; US04981953 Immunotoxins, process for their preparation and pharmaceutical compositions in which they are present; US04980457 Cytotoxic conjugates which can be used in therapy and process or their preparation; US04545985 Pseudomonas exotoxin conjugate immunotoxins; US06020145 Methods for determining the presence of carcinoma using the antigen binding region of monoclonal antibody BR96; US05792458 Mutant diphtheria toxin conjugates; US05106956 Ribosome-inactivating glycoproteins, modified by oxidation of their osidic units and reduction, and in vivo prolonged-action immunotoxins containing such a glycoprotein; US05104976 Ribosome-inactivating glycoproteins, modified by oxidation of their osidic units and formation of a Schiff's base and in-vivo prolonged action immunotoxins containing such a Glycoprotein; WO00061132A1 US04894225 Combination therapy using antitumor immunotoxins with tumor necrosis factor; US05338542 Disulfide linked immunotoxins with molecular COMPOSITIONS CONTAINING IMMUNOTOXINS AND AGENTS THAT INHIBIT DENDRITIC CELL MATURATION FOR INDUCING IMMUNE TOLERANCE TO A GRAFT; US04894227 Composition of groupings in the linker which cause steric hindrance to thedisulfide linkage; US04863726 Combination therapy using immunotoxins with interleukin-2; immunotoxins with interleukin-2 US04762707 New conjugates associating, by covalent bond, an enzyme with an antibody, and medicinal associations using the said conjugates; USRE036866 Anti-aids immunotoxins; US06099842 Recombinant immunotoxin composed of a single chain antibody reacting with the human transferrin receptor and diptheria toxin US06071519 Immunotoxins specific for CD86 expressing cells; US06042829 Biotherapy of cancer by targeting TP-3/P80; US06004554 Methods for targeting the vasculature of solid tumors; WO09839363A2 IMMUNOTOXINS AND METHODS OF INDUCING IMMUNE TOLERANCE; US05792456 Mutant BR96 antibodies reactive with human carcinomas; US05728821 Mutant BR96 antibodies reactive with human carcinomas; US05208021 Method of US05728383 Treatment of tumors of the central nervous system with immunotoxins; US05916772 Recombinant production of saporin-containing Proteins; preparing diphtheria immunotoxins; US05144009 Conjugates in which a monovalent carboxylic ionophore WO09818820A1 METHODS AND COMPOSITIONS FOR RICIN FUSION PROTEIN IMMUNOTOXINS TO TREAT CANCER AND AUTOIMMUNE DISEASE; US04916213 Ribosomal inhibiting protein-immunoglobulin conjugates with is associated by means of a covalent bond with a macromolecule, their use as immunotoxin potentiators and the intermediate activatedinophores; US06015555 Transferrin receptor specific specificity for tumor cell surface antigens, and mixtures thereof; US05977307 Transferrin receptor specificligand-antibody-neuropharmaceutical or diagnostic agent conjugates; US05770196 neuropharmaceutical agent fusion proteins; US05821123 Modified antibody variable domains; US05766886 Modified antibody variable Modified antibody variable domains and therapeutic uses thereof; US05112607 Potentiation of domains; US05672683 Transferrin neuropharmaceutical agent fusion protein; US04753894 Monoclonal immunotoxin action by Brefeldin A; US04902495 IgE Fc directed delivery system; US04485093 Immunotoxin conjugate which comprises arsanilic acid, anti-human breast cancer antibodies; US06103235 Methods of inducing immune useful for treating malignant tumors, particularly pancreatic Cancer; WO09964073A2 RECOMBINANT IMMUNOTOXIN DIRECTED AGAINS THE HIV-1 tolerance using immunotoxins; WO09948914A1 METHODS FOR USING HEAT SHOCK PROTEINS; GP120 ENVELOPE GLYCOPROTEINs; WO09904807A1 RECOMBINNANT IMMUNOTOXIN US05869619 Modified antibody variable domains; WO09713529A1 IMMUNOTOXIN CONTAINING A DIPHTERIAL TOXIN AND INTERLEUKIN -2(DT482-IL2) AND METHOD FOR PREPARING THE SAME; WO09858678A1 ANTI-CD40L IMMUNOTOXINS FOR THE TREATMENT OF DISEASES; US05645836 Anti-AIDS immunotoxins; US05439815 Restrictocin-like ribotoxin analogues comprising only one cysteine available for covalent linkage to a partner; US05149782 Molecular conjugates containing cell membrane-blending agents; WO09855150A1 TXU-7-PAP IMMUNOTOXIN AND USE THEREOF; WO09713529A1 IMMUNOTOXIN CONTAINING A DISULFIDE-STABIL ANTIBODY FRAGMENT; US06184043 Method for detection of specific target cells in specialized or mixed cell population and solutions containing mixed cell populations; US06147203 Recombinant disulfide-stabilized polypeptide fragments having binding specificity; WO0040270A2 METHODS OF PROLONGING TRANSPLANT SURVIVAL USING IMMUNOTOXINS AND COSTIMULATION BLOCKADE OF CD154 AND D28; WO00040265A1 POTENTIATION OF ANTI-CD38-IMMUNOTOXIN CYTOTOXICITY; US06087109 Compositions that specifically bind to colorectal cancer cells and methods of using the same; US06060037 Compositions that specifically bind to colorectal cancer cells and methods of using the same; WO09953954A1 USE OF IMMUNOTOXINS TO INDUCE IMMUNE TOLERANCE TO PANCREATIC ISLET TRANSPLANTATION; US05928873 Methods of and kits and compositions for diagnosing colorectal tumors and metastasis thereof; US05879656 Methods of treating metastatic colorectal cancer with ST receptor binding compounds; US05863538 Compositions for targeting the vasculature of solid tumors; US05833988 Transferrin receptor specific antibody-neuropharmaceutical or diagnostic agent conjugates; US05759546 Treatment of CD4 T-cell mediated conditions; US05731159 Methods of and kits and compositions for diagnosing colorectal tumors and metastasis thereof; US05677171 Monoclonal antibodies directed to the HER2 receptor; US05601990 Methods of diagnosing colorectal tumors and metastasis thereof; US05518888 ST receptor binding compounds and methods of using the same; US05045451 Methods for screening antibodies for use as immunotoxins; US04865841 Methods and compositions for transient elimination of humoral immune antibodies; US04831122 Radioimmunotoxins; US04771128 Method of purifying toxin conjugates using hydrophobic interaction chromatography; US04582703 Cytotoxic medicament formed from the association of at least one immunotoxin and chloroquin; US05651986 Controlled local delivery of chemotherapeutic agents for treating solid tumors; US05644033 Monoclonal antibodies that define a unique antigen of human B cell antigen receptor complex and methods of using same for diagnosis and treatment; US05332567 Detection and treatment of

infections with immunoconjugates; US04767621 Drugs comprising in association at least one immunotoxin and at least one monovalent carboxylic ionophore; US06093399 Methods and compositions for the specific coagulation of vasculature; US06036955 Kits and methods for thespecific coagulation of vasculature; US06004555 Methods for the specific coagulation of vasculature; US05939531 Recombinant antibodies specific for a growth factor receptor; US5877289 Tissue factor compositions and ligands for specific coagulation of vasculature; WO09856823A1 INDUCTION OF IMMUNE TOLERANCE BY IMMUNOTOXIN; WO09850435A1IMMUNOTOXINS, COMPRISING AN ONC PROTEIN, DIRECTED AGAINST MALIGNANT CELLS; US05830478 Method for delivering functional domains of diphtheria toxin to a cellular target; US05777078 Triggered pore-forming agents; WO09733611A1 METHOD OF KILLING TARGET CELLS IN HARVESTED CELL POPULATIONS WITH ONE OR MORE IMMUNOTOXINS; US05629197 Monoclonal anti-human breast cancer antibodies;*US05470831 1/28/1995 Angiogenic peptides; US05352447 Immunotoxins for treatment of intracranial lesions and as adjunct to chemotherapy; JP02169523A2 IMMUNOTOXIN FOR TREATMENT OR PREVENTION OF AUTOIMMUNE DISEASE US04917888 Solubilization of immunotoxins for pharmaceutical compositions using polymer conjugation; US04904481 Method of conferring immuno-tolerance to a specific antigen; US06187536 Methods of identifying and detecting pancreatic cancer; US06165464 Monoclonal antibodies directed to the HER2 receptor; US06121424 Multivalent antigen-binding proteins; US06103889 Nucleic acid molecules encoding single-chain antigen-binding proteins; US06096862 Multimeric antiviral agent; EP01000357A1 EP01005372A1 ANTI-CD40L IMMUNOTOXINS FOR THE TREATMENT OF DISEASES; EP01000357A1 ANTIBODIES AND SCFV IMMUNOTOXINS SPECIFIC TO IMPORTED FIRE ANTS, AND THEIR APPLICATION; EP00996467A1 TXU-7-PAP IMMUNOTOXIN AND USE THEREOF; US06051230 Compositions for targeting the vasculature of solid tumors; US06033876 Anti-CD30 antibodies preventing proteolytic cleavage and release of membrane-bound CD30 antigen; US06027725 Multivalent antigen-binding proteins; US06025165 Methods for producing multivalent antigen-binding proteins; US05990296 Single chain B3 antibody fusion proteins and their uses; US05990275 Linker and linked fusion polypeptides; US05981726 Chimeric and mutationally stabilized tumor-specific B1, B3 and B5 antibody fragments; immunotoxic fusion proteins; and uses thereof; US05965132 Methods and compositions for targeting the vasculature of solid tumors; US05889157 Humanized B3 antibody fragments, fusion proteins, and uses thereof; WO09902991A1 ANTIBODIES AND SCFV IMMUNOTOXINS SPECIFIC TO IMPORTED FIRE ANTS, AND THEIRAPPLICATION; US05855866 Methods for treating the vasculature of solid tumors; EP00717753B1 RIBOSOME INACTIVATING PROTEINS EXTRACTED FROM SEEDS OF SAPONARIA OCYMOIDESAND VACCARIA PYRAMIDATA, THEIR PREPARATION AND IMMUNOTOXINS CONTAINING THEM; US05824311 Treatment of tumors with monoclonal antibodies against oncogene antigens; EP00861091A1 IMMUNOTOXIN CONTAINING A DISULFIDE-STABILIZED ANTIBODY FRAGMENT; US05786457 Hormone-nuclease compounds and method for regulating hormone related diseases; US05776427 Methods for targeting the vasculature of solid tumors; US05772997 Monoclonal antibodies directed to the HER2 receptor; EP00831917A2 IMMUNOTOXINS SPECIFIC FOR CD80 AND CD86 EXPRESSING CELLS; EP00820470A1 NOVEL ANTI-AIDS IMMUNOTOXINS; US05707964 Method for treating cancer; US05705157 Methods of treating cancerous cells with anti-receptor antibodies; US05690935 Biotherapy of cancer by targeting TP-3/P80; US05665357 Antibodies recognizing tumor associated antigen CA 55.1; US05660827 Antibodies that bind to endoglin; US05631229 Method for inactivating gonadotrophs; US05608039 Single chain B3 antibody fusion proteins and their uses; US05576288 Fibroblast growth factor conjugates; US05571894 Recombinant antibodies specific for a growth factor receptor; US05529932 Isolated DNA encoding a plant ribosome inactivating protein from the leaves of saponaria officinalis; US05527527 Transferrin receptor specific antibody-neuropharmaceutical agent conjugates; US05506343Antibodies specific for the DF3 carcinomaassociated antigen; US05492893Hormone-toxin conjugate compounds; US05491088Monoclonal antibody BR 96 and chimeric monoclonal antibodies having the variable region of MAB BR96, which bind to a variant of ley antigen on human carcimona cells; US05489525Monoclonal antibodies to prostate cells; US05488036 Method for sterilizing animals usinghormone-toxin conjugate compounds; JP07126187A2CARCINOSTATIC AGENT; US05393737Cytotoxic drug conjugates for treatment ofneoplastic diseases; US05378688GnRH analogs for destroying gonadotrophs; US05306626Process for production of restrictocin; EP00583794A1Recombinant pseudomonas exotoxin: construction of an active immunotoxin with low side effects; EP00577612A1IMMUNOTOXIN FROM ANTI-CD5 MONOCLONAL ANTIBODIES; EP00561953A1 RECOMBINANT IMMUNOTOXIN COMPOSED OF A SINGLE CHAIN ANTIBODY REACTING WITH THE HUMAN TRANSFERRIN RECEPTOR ANDDIPHTHERIA TOXIN; US05167956 Immunotoxin with in-vivo T cell suppressantactivity; EP00365087B1Immunotoxins for the treatment or prophylaxisof auto-immune diseases; EP00192002B1Prolonged acting immunotoxins comprising a ribosome inactivating glycopeptide constituent having modifiedpolyssaccharide moieties; JP04069345A2METHOD FOR REMOVING TUMOROUS CELL; EP00255424B1Immunotoxins, process for preparing them andpharmaceutical compositions containing them; US05024834Thioether linked immunotoxin conjugates; EP00214995B1 IMMUNOTOXIN AND METHOD OF MAKING; EP00234151B1Glycoproteins modified by oxidation and formation of Schiff bases, inhibiting ribosomes, process for obtaining the same, and immunotoxines containingsuch glycoprotein; EP00229564B1Glycoproteins modified by oxidation followedby reduction, which inhibit ribosomes, production process andimmunotoxines containing such a glycoprotein; EP00327169A3Immunotoxins from barley toxin; EP00365087A1Immunotoxins for the treatment or prophylaxisof auto-immune diseases; US04913907Porphycene anti-cancer agents and treatment methods; US04894226Solubilization of proteins for pharmaceuticalcompositions using polyproline conjugation; EP00327169A2Immunotoxins from barley toxin; US04806494Monoclonal antibody against ovarian cancer cells (OVB-3); EP00255424A1Immunotoxins, process for preparing them andpharmaceutical compositions containing them; US04698420Antibody hybrid molecules and process for their preparation; EP00234151A1Glycoproteins modified by oxidation and formation of Schiff bases, inhibiting ribosomes, process for obtaining the same, and immunotoxines containingsuch glycoprotein; EP00229564A1 Glycoprotein modified by oxidation and reduction,

inhibiting the ribosomes, method for its production and immunotoxins contaning said glycoprotein; US04681760Method of conferring immunotolerance to aspecific antigen; EP00214995A1 IMMUNOTOXIN AND METHOD OF MAKING; US04614650Cytotoxic composition including at least an immunotoxine and an amine; EP00192002A1Prolonged acting immunotoxins comprising aribosome inactivating glycopeptide constituent having modifiedpolyssaccharide moieties; EP00086152B1Medicines containing an association of atleast one immunotoxine and at least one monovalent carboxylicionophore; EP00086152A1Medicines containing an association of atleast one immunotoxine and at least one monovalent carboxylicionophore; US06171588Anti-.alpha.vࢹ integrin antibody antagonists; US06156564Cellular apoptosis susceptibility protein (CSP)and antisense CSP; US06156321Tissue factor methods and compositions forcoagulation and tumor treatment; US06143869CD30 ligand oligomers and polypeptides; US06132730Combined tissue factor and factor VIIa methodsand compositions for coagulation and tumor treatment; US06132729Combined tissue factor and chemotherapeuticmethods and compositions for coagulation and tumor treatment; WO00058456A2COMPOSITIONS AND METHODS FOR MODIFYING TOXICEFFECTS OF PROTEINACIOUS COMPOUNDS; US06107461Multimeric forms of human rhinovirus receptorand fragments thereof, and method of use; US06086900Methods and compositions for usingmembrane-penetrating proteins to carry materials across cellmembranes; US06072031Cellular apoptosis susceptibility protein(CSP); EP00610286B1RECOMBINANT IMMUNOTOXINS; US06017896Purine nucleoside phosphorylase gene therapyfor human malignancy; US05998587Anti-cyanovirin antibody; US05985553erbB-2 gene segments, probes, recombinant DNAand kits for detection; US05977322High affinity human antibodies to tumorantigens; WO09948534A1METHODS AND MEANS FOR THE TREATMENT OF IMMUNERELATED DISEASES; US05928643Method of using CD2-binding domain oflymphocyte function associated antigen 3 to initiate T cellactivation; US05919764Compounds that bind to p185 and methods ofusing the same; US05914111CD2-binding domain of lymphocyte functionassociated antigen-3; US05911995EGF-genistein conjugates for the treatment ofcancer; US05910424Metastatic melanoma cell lines from monodelphisdomestica for use in anti-cancer agent discovery; US05869620Multivalent antigen-binding proteins; US05861156Methods of delivering agents to target cells; WO09855623A1TYPE-1 RIBOSOME-INACTIVATING PROTEIN; US05846565Controlled local delivery of chemotherapeuticagents for treating solid tumors; US05843462Diphtheria toxin epitopes; US05843425Transplantation and graft-versus-host-disease; US05824776Cell-targeted lytic pore-forming agents; US05821081Nucleic acids encoding antiviral proteins andpeptides, vectors and host cells comprising same, and methods ofproducing the antiviral proteins and peptides; US05817771Cell-targeted lytic pore-forming agents; WO09831394A2TISSUE FACTOR METHODS AND COMPOSITIONS FORCOAGULATION AND TUMOR TREATMENT; WO09828298A1RICIN INHIBITORS AND METHODS FOR USETHEREOF; US05759782Cellular apoptosis susceptibility protein (CSP)and antisense CSP; WO09817116A1TARGETED CYTOTOXIC CELLS; US05736536Method for treating vascular leak syndrome; US05728677Methods of inhibiting T-cell dependentproliferation of peripheral blood lymphocytes using the CD2-bindingdomain of lymphocyte function associated antigen 3; US05728579DNA encoding Mat-8; US05723326Genome coding phytolacca antiviral protein anda recombinant expression vector therefor; US05697902Method for imaging and treating organs andtissues; US05677430Antibodies directed against CD30 ligand; US05670151Method for controlling hyperproliferativediseases; US05667786Method for treating tumors with a toxin; US05663144Compounds that bind to p185 and methods ofusing the same; WO09727871A1METHOD OF INACTIVATION OF RAS SUBFAMILYPROTEINS AND AGENTS THEREFOR; US05648234Expression vector for Phytolacca antiviralprotein; US05639863Human monoclonal antibodies specific to cellcycle independent glioma surface antigen; US05632990Treatment for tumors comprising conjugatedantibody A5B7 and a prodrug; US05626862Controlled local delivery of chemotherapeuticagents for treating solid tumors; US05624827DNA sequences encoding the plant toxingelonin; US05621083Immunotoxins comprising ribosome-inactivatingproteins; US05616122Methods and compositions for preventingsecondary cataracts; US05597569Bryodin 2 a ribosome-inactivating proteinisolated from the plant Bryonia dioica; WO09701636A2RECOMBINANT MISTLETOE LECTIN; US05552311Purine nucleoside phosphorylase gene therapyfor human malignancy; US05547853CD2-binding domain of lymphocyte functionassociated antigen 3; EP00717753A1RIBOSOME INACTIVATING PROTEINS EXTRACTED FROMSEEDS OF SAPONARIA OCYMOIDESAND VACCARIA PYRAMIDATA, THEIRPREPARATION AND IMMUNOTOXINS CONTAINING THEM; EP00700444A1IMMUNOTOXINS COMPRISING GELONIN AND ANANTIBODY; US05480981CD30 ligand; US05478804Treatment of tumorigenic pathophysiological conditions with FGF-cytoxic conjugates; US05455030Immunotheraphy using single chain polypeptidebinding molecules; EP00635030A1IMMUNOTOXINS DIRECTED AGAINST c-erbB-2(HER-2/-i(neu)) RELATED SURFACE ANTIGENS; EP00634938A1IMMUNOTOXINS DIRECTED AGAINST CD33 RELATEDSURFACE ANTIGENS; JP06312942A2CARCINOSTATIC AGENT FOR HUMAN HEPATOMA CELLPRODUCING ALPHA-FETOPROTEIN; US05348865Genome coding phytolacca antiviral protein anda recombinant expression vector therefor; EP00610286A1RECOMBINANT IMMUNOTOXINS; EP00261671B1Recombinant pseudomonas exotoxin:construction of an active immunotoxin with low side effects; US05283344Coupling method using selective amination ofmaleimide; US05191067Fibroblast growth factor conjugates; EP00303681B1IMMUNOSUPPRESSION IN IMMUNOTOXIN BASED HUMANTHERAPY; EP00226418B1Anti-human ovarian cancer immunotoxins andmethods of use thereof; EP00226419B1Anti-human ovarian cancer immunotoxins andmethods of use thereof; US05090914Activated polymers and conjugates thereof; US05055289Interferon antibody therapeutic compositionshaving an extended serum half-life; JP03130235A2ANTITUMOR AGENT; US04997913pH-sensitive immunoconjugates and methods fortheir use in tumor therapy; US04977280Conjugates in which a monovalent carboxylicionophore is associated by means of a covalent bond with amacromolecule, their use as immunotoxin potentiators and theintermediate activated ionophores; US04918927Process for the potentiation of immunotoxins; US04911690Treatment or diagnosis by endoscopicadministration into the lymphatics; EP00186551B1Medicament containing as a mixture at leastone immunotoxin and at least one polymer containing mannose; JP02019324A2MONOCLONAL ANTIBODY AGAINST

OVARIAN CELL; EP00162781B1Conjugates associated with a covalent bond toa monovalent carboxylic ionophore and a macromolecule, their use aspotentializers of immunotoxines andthe activated intermediateionophores; JP01102032A2IMMUNOTOXIN TREATMENT FOR ALLERGY; EP0030368 1A1IMMUNOSUPPRESSION IN IMMUNOTOXIN BASED HUMANTHERAPY; US04792447Anti-immunoglobulin toxin conjugates useful inthe treatment of B cell tumors; EP00261671A2Recombinant pseudomonas exotoxin:construction of an active immunotoxin with low side effects; EP00256714A2Combination therapy using anti-tumormonoclonal antibodies and/or immunotoxins with interleukin-2; EP00232447A1Lectin immunotoxins; EP00089270B1Cytotoxic medicines containing at least oneimmune toxine and one amine; EP00226419A 2 Anti-human ovarian cancer immunotoxins andmethods of use thereof; EP00226418A2Anti-human ovarian cancer immunotoxins andmethods of use thereof; EP00186551A1Medicament containing as a mixture at leastone immunotoxin and at least one polymer containing mannose; EP00088694B1Cytotoxic medicine containing at least oneimmune toxine and chloroquine; EP00162781A1Conjugates associated with a covalent bond toa monovalent carboxylic ionophore and a macromolecule, their use aspotentializers of immunotoxines andthe activated intermediateionophores; EP00130132A1Antitumour immunotoxin; pharmaceuticalcompositions containing it, and itsuse in vitro; US06187810Macrocyclic compounds made from suboxideunits; EP01073463A1 USE OF IMMUNOTOXINS TO INDUCE IMMUNETOLERANCE TO PANCREATIC ISLET TRANSPLANTATION; US06177554Nucleic acid transporter systems; US06177280Ricin inhibitors and methods for use thereof; US06165750Modified-affinity streptavidin; US06159947Anti-RAS intracellular binding proteins and usethereof; US06156541Compositions and methods for catalyzinghydrolysis of HIV gp120; US06156493Modified-affinity streptavidin; US06150168Nucleic acid transporter systems and methods ofuse; US06146628Biotherapeutic agents comprising recombinantPAP and PAP mutants; US06143298Soluble truncated forms of ICAM-1; US06127170Multifunctional complexes for gene transferinto cells comprising a nucleic acid bound to a polyamine and havinga endosome disruption agent; US06123939Anti-neoplastic drugs in cancer therapy; US06120767Chimeric antibody with specificity to human Bcell surface antigen; US06117673RDGB proteins and related products andmethods; US06110735Method for the preparation of a viral vector byintermolecular homologous recombination; US06103233Cellular and serum protein anchors andconjugates; US06096303Method to enhance treatment of cystic tumors; US06093692Method and compositions for lipidization ofhydrophilic molecules; US06089234 7/18/2000 Method for destroying residual lens epithelialcells; EP01015496A2IMMUNTOXINS AND METHODS OF INDUCING IMMUNETOLERANCE; US06084084 Human metabotropic glutamate receptor; US06077675Human metabotropic glutamate receptor; US06074836Method of marking eukaryotic cells; US06071493Method of screening for an agent that inhibitsmononuclear phagocyte-plaque component complex formation; US06066470Method for removing N-terminal methionine; US06060066Method for treating tumors with a toxin; US06056959CD40 antigen antibody complex; US06051688Isolated human metabotropic glutamate receptorMglur-8; US06051231Antiviral methods and prepations; US06048717Inhibitors of catalytic antibodies; US06043283Tyramine compounds and their neuronal effects; US06039684Non-lethal conditioning methods for thetreatment of acquired immunodeficiency syndrome; US06037329Compositions containing nucleic acids andligands for therapeutic treatment; US06033884Nucleic acid transporter systems and methods ofuse; US06031003Calcium receptor-active molecules; WO00006194A2DEPLETION OF CELLS RESPONSIBLE FORANTIBODY-MEDIATED GRAFT REJECTION; EP00975674A1IMMUNOTOXINS, COMPRISING AN ONC PROTEIN,DIRECTED AGAINST MALIGNANT CELLS; US06018096Animal model for engraftment, proliferation anddifferentiation of human hematopoietic stem cells; US06015876Method of using cyanovirins; US06015556Cytotoxic drug therapy; US06011068Calcium receptor-active molecules; US06004812In-vitro T-lymphopoiesis system; US06004552Methods of blocking B cell proliferation usinganti-CD40 monoclonal antibodies; US06001991Antisense oligonucleotide modulation of MDRP-glyceprotein gene expression; US05994109Nucleic acid transporter system and methods ofuse; US05990286Antibodies with reduced net positive charge; US05981505Compositions and methods for delivery ofgenetic material; US05976535Pretargeting protocols for the enhancedlocalization of cytotoxins to target sites and cytotoxiccombinations useful therefore; US05972901 Serpin enzyme complex receptor--mediated genetransfer; US05972900Delivery of nucleic acid to cells; US05962653Methods of obtaining antiviral proteins andantiviral peptides from Nostoc ellipsosporum; US05962428Compositions and methods for delivery ofgenetic material; US05962314 Calcium receptor-active molecules; US05958770Glycoalkaloids; JP11253181A2RECOMBINANT PSEUDOMONAS EXOTOXIN: ACTIVEIMMUNOTOXIN STRUCTURE OF LOW SIDE EFFECTS; US05948635Totally Synthetic Affinity Reagents; US05945100 8/31/1999 Tumor delivery vehicles; US05939070Hybrid botulinal neurotoxins; US05922847Methods of purifying hematopoietic cells usingan antibody to a stem cell factor receptor; US05919457TXU-5/B53-PAP antiviral US05919911Monoclonal antibodies to stem cell factorreceptors; US05917021Stabilized monomeric protein compositions; biotherapeutic agentfor the treatment of AIDS; US05916803 Target cell-specific non-viral vectors forinserting genes into cells, pharmaceutical compositions US05916561Monoclonal antibody against CD44v6; US05914127Isolation comprisingsuch vectors and their use; US05910486Methods for modulating protein function incells using, intracellular antibody and uses of caveolae; US05906938Method of reconstituting hematopoietic cellsusing monoclonal antibodies to the stem cell homologues; US05891689Heme-bearing microparticles for targeteddelivery of drugs; factor receptor; US05877210Phosphotyrosine phosphatase inhibitors orphosphotyrosine kinase activators for controlling US05874082Humanized anti-CD40 monoclonal cellularproliferation; US05877162Short external guide sequences; US05874081Therapeutic compositions and antibodies andfragments capable of blocking B cell proliferation; US05871733Multimeric forms of human methods forinhibition and treatment of tumor associated angiogenesis; US05866570Treatment of vascular leakage and relatedsyndrome such as septic shock rhinovirus receptorprotein; US05863540Adhesion molecule; US05858687Cell bioassay of by administration of metalloproteinaseinhibitors; US05856456Linker for linked neurotoxins; US05858684Method of screening calcium receptor-activemolecules; US05854027Process for fusion polypeptides; US05854400Monoclonal antibodies which neutralize HIV-1infection; US05851991Therapeutic use improving the stability ofantibodies; US05852167Totally synthetic affinity reagents;

of the retinoblastomasusceptibility gene product; US05847121Production of nitro-benzyl-dota via directpeptide cyclization; US05846535Methods for reducing tumor cell growth by usingantibodies with broad tumor reactivity and limited normal tissuereactivity; US05844076Totally synthetic affinity reagents; US05843893Method for inhibiting the proliferation ofepithelial lens cells and implantable lens therefor; US05843882Antiviral proteins and peptides; US05843724Chimeric nucleic acids and proteins forinhibiting HIV-1 expression; US05843685Production of chimeric mouse-human antibodieswith specificity to human tumor antigens; US05840854Monoclonal antibody BR110 and uses thereof; US05840300Methods and compositions comprising singlechain recombinant antibodies; US05837846Biosynthetic binding proteins forimmuno-targeting; US05837533Complexes comprising a nucleic acid bound to acationic polyamine having an endosome disruption agent; US05837283Cationic lipid compositions targetingangiogenic endothelial cells; US05834599Immunoconjugates which neutralize HIV-1infection; US05833985Bispecific molecules for use in inducingantibody dependent effector cell-mediated cytotoxicity; US05831036Soluble fragments of human intercellularadhesion molecule-1; US05830876Genetic immunization; US05827934Cytotoxic diphtheria toxin fragments; US05827655 Assay, methods and products based on n K+channel expression; US05824805Branched hydrazone linkers; US05817637Genetic immunization; US05817310Inhibitory immunoglobulin polypeptides to humanPDGF beta receptor; US05789554Immunoconjugates and humanized antibodiesspecific for B-cell lymphoma and leukemia cells; US05773245Methods for increasing secretion ofoverexpressed proteins; US05770195Monoclonal antibodies directed to the her2receptor; US05767073D4 gene and methods of use thereof; US05763733 Antigen-binding fusion proteins; US05763569 Calcium receptor-active molecules; US05762921Composition and methods for the treatment oftumors; US05759517Hemoglobins as drug delivery agents; US05756097Lymphokine activated effector cells forantibody-dependent cellular cytotoxicity (ADCC) treatment of cancerand other diseases; JP10136988A2RECOMBINANT PSEUDOMONAS EXOTOXIN: STRUCTUREOF ACTIVE IMMUNOTOXIN HAVING LESS SIDE EFFECT; US05753204Biosynthetic binding proteins forimmunotargeting; US05753203CD30 ligand conjugates; US05747334Random peptide library; US05744335Process of transfecting a cell with apolynucleotide mixed with an amphipathic compound and a DNA-bindingprotein; US05744315Compounds from biopolymers and effectorsubstances which are linked via optically active amino acidderivatives, processes for the preparation thereof and the usethereof; US05739118Compositions and methods for delivery ofgenetic material; EP00830146A2METHODS OF INDUCING IMMUNE TOLERANCE USINGIMMUNOTOXINS; US05725856Monoclonal antibodies directed to the HER2receptor; US05725855Method of treating tumors with CD8+ -depletedor CD4+ T cell subpopulations; US05721108Chimeric antibody with specificity to human Bcell surface antigen; US05720954Monoclonal antibodies directed to the HER2receptor; US05720937 In vivo tumor detection assay; US05720720Convection-enhanced drug delivery; US05718899Method and compositions for direct concentrateddelivery of passive immunity; US05716990Drug delivery systems; US05709995Hepatitis C virus-derived peptides capable ofinducing cytotoxic T lymphocyte responses; US05707627Methods and compositions for the directconcentrated delivery of passive immunity; US05695760Modified anti-ICAM-1 antibodies and their usein the treatment of inflammation; US05693627Use of phosphotyrosine phosphatase inhibitorsfor controlling cellular proliferation; US05690928Method of treating bladder cancer cells; US05688938Calcium receptor-active molecules; US05686582Multimeric forms of human rhinovirus receptorprotein; US05686581Multimeric form of human rhinovirus receptorprotein; US05683694Method for the treatment of tumors withconjugated antibody A5B7 and a prodrug; US05683692Use of RIPonucleases for treating parasitic andviral diseases; US05681810Diphtheria toxin fragments, conjugates andmethods of use to inhibit tumors and leukemia; US05681565Methods and compositions for passiveimmunotherapy; US05679777Hemoglobins as drug delivery agents; US05677274Anthrax toxin fusion proteins and relatedmethods; US05677165Anti-CD40 monoclonal antibodies capable ofblocking B-cell activation; US05676924In vivo assay to determine cancer treatmenteffectiveness; US05674982Multimeric form of human rhinovirus receptorprotein; US05663306Method of conjugating an activated ester to anamine-containing biological material; US05658753Catalytic antibody components; US05658568Cytotoxic drug therapy; US05654267Cooperative combinations of ligands containedwithin a matrix; US05645835Therapeutic antibody based fusion proteins; US05641677Method of enhancing the immunotherapeuticactivity of immune cells by depletion of CD8+ T cells; US05625033Totally synthetic affinity reagents; US05621002Prodrugs for enzyme mediated activation; US05620013Method for destroying residual lens epithelialcells; US05616458Tripterygium wilfordii hook F extracts andcomponents, and uses thereof; US05614611Humanized monoclonal antibodies binding tolgE-bearing B cells but not basophils; US05612216Nucleotide sequence encoding intercellularadhesion molecule-1 and fragments thereof; US05602015Autoantibodies which enhance the rate of achemical reaction; US05601827Diphtheria toxin vaccines; US05599538Autoantibodies which enhance the rate of achemical reaction; US05593972Genetic immunization; US05591631Anthrax toxin fusion proteins, nucleic acidencoding same; US05589453Human rhinovirus receptor protein (ICAM-1) thatinhibits rhinovirus attachment and infectivity; WO09641608A2PYRULARIA THIONIN CONTAINING IMMUNOTOXINS ANDIMMUNOTOXIN-LIKE CONJUGATES; WO09640260A2IMMUNOTOXINS SPECIFIC FOR CD80 AND CD86EXPRESSING CELLS; US05585478D4 gene and methods of use thereof; US05583242Use of phosphotyrosine phosphatase inhibitorsfor controlling cellular proliferation; US05582996Bifunctional antibodies and method of preparingsame; 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D6, an antibody which binds intercellularadhesion molecule-1; US05453271Vaccine against ricin toxin; US05422339 6/06/1995 Peptides having insulin autoantibody but notinsulin receptor binding capacity; US05420011Cell bioassay for neurotoxins; US05416202Materials comprising and methods of preparationand use for ribosome-inactivating proteins; US05405966Trichothecene conjugates; WO09507297A1RIBOSOME INACTIVATING PROTEINS EXTRACTED FROMSEEDS OF SAPONARIA OCYMOIDES AND VACCARIA PYRAMIDATA, THEIRPREPARATION AND IMMUNOTOXINS CONTAINING THEM; WO09503828A1SINGLE-CHAIN IMMUNOTOXIN COMPOSITIONS ANDMETHODS FOR PREVENTING SECONDARY CATARACTS; WO09503783A1POLYMERIC DEVICE FOR THE DELIVERY OFIMMUNOTOXINS FOR THE PREVENTION OF SECONDARY CATARACT; US05387578New linker for bioactive agents; US05376546Analogs of ribosome-inactivating proteins; WO09426910A1IMMUNOTOXINS COMPRISING GELONIN AND ANANTIBODY; WO09421813A1MONOCLONAL ANTIBODIES SPECIFIC FOR FIBROBLASTGROWTH FACTOR RECEPTORS, IMMUNOTOXINS, AND USE THEREOF; 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WO08806451A1 IMMUNOSUPPRESSION IN IMMUNOTOXIN BASED HUMANTHERAPY; US04766106 Solubilization of proteins for pharmaceuticalcompositions using polymer conjugation; US04744981 Trichothecene antibody conjugates; WO08802401A1 RECOMBINANT PSEUDOMANAS EXOTOXIN:CONSTRUCTION OF AN ACTIVE IMMUNOTOXIN WITH LOW SIDE EFFECTS; US04672107 Cell growth inhibitor and method; US04664911 Immunotoxin conjugates employing toxin B chainmoieties; WO08605098A1 IMMUNOTOXIN AND METHOD OF MAKING; US04590071 Human melanoma specific immunotoxins; US04585742 Monoclonal antibody with specificity to humansmall cell carcinoma and use thereof; EP00129434A2 Immunotoxin conjugates; WO08303200A1 CYTOTOXIC MEDICINES INCLUDING AT LEAST ANIMMUNOTOXINE AND AN AMINE; WO08303055A1 CYTOTIXIC DRUG FORMED BY THE ASSOCIATION OFAT LEAST ONE IMMUNOTOXINE AND CHLOROQUINE; WO08302725A1 DRUGS COMPRISING AS ASSOCIATION AT LEAST ONEIMMUNOTOXIN AND AT LEAST ONE MONOVALENT CARBOXYLIC IONOPHORA; Koon HB, Junghans RP. 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amplifiednucleic acid sequences and cellular antigens in cells; US05843446 Immunogenic LHRH peptide constructs andsynthetic universal immune stimulators for vaccines; US05837510 Methods and polynucleotide constructs fortreating host cells for infection or hyperproliferative disorders; US05830850 Methods for the treatment of bone resorptiondisorders, including osteoporosis; US05827819 Covalent polar lipid conjugates withneurologically active compounds for targeting; US05827516 Immunomodulatory peptides; US05820866 Product and process for T cell regulation; US05817315 Recombinant vaccine; US05800980 Detection of MSRV1 virus and MSRV2 pathogenand/or infective agent associated with multiple sclerosis, bynucleic acid hybridization; US05776746 Gene amplification methods; US05773253 MYPPPY variants of CTL A4 and uses thereof; US05759551 Immunogenic LHRH peptide constructs andsynthetic universal immune stimulators for vaccines; US05728540 Cytotoxic factor as is associated with multiplesclerosis, its detection and its quantification; WO09807441A1 ALLOGENEIC HISTOCOMPATIBILITY COMPLEXES ASMEDIATORS OF CELL DESTRUCTION; US05705732 Universal donor cells; US05693522 Anti-cancer immunotherapeutics; US05679784 Recombinant mutants for inducing specificimmune responses; US05679345 Method for preventing complement-dependentrejection of organ or tissue transplants; US05658568 Cytotoxic drug therapy; US05624895 Treatment and/or prevention of type I diabetesmellitus with gamma interferon administration; US05409825 Expansion of human hematopoietic progenitorcells in a liquid medium; US05002869 Monoclonal antibody specific to a determining the presence and titersof anti HIV-1 ag27bodies; US06143298Soluble truncated forms of ICAM-1 novel epitopeof the LFA-1 antigen of human T lymphocytes; US05288854Functional derivatives of ICAM-1 which are substantially capable of binding to LFA-1...US05962424Methods and compositions for targeting selectinsUS05852175P-selectin glycoprotein ligand blocking antibodiesUS05800815Antibodies to P-selectin and their uses; US06130202Antiviral methods; US06033667Method for detecting the presence of P-selectin US05880091Glycoprotein ligand for P-selectin and methods of use thereof US05612216Nucleotide sequence encoding intercellular adhesion molecule-1 and fragments thereof US05891841Methods of using intercellular adhesion molecule-3 (ICAM-3)...US05605821Expression control sequences of the P-selectin gene US05977080Sulfated disaccharide inhibitors of selectins,...US05834425Use of chimeric selectins as simultaneous blocking agents... 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Carbohydrate conjugates as inhibitors of celladhesion; US05811405 Multiply fucosylated dicarboxylic acidspossessing antiadhesive properties; US05654282 Selectin binding glycopeptides; US05632991 Antibodies specific for E-selectin and the usesthereof; US05599676 Method for isolating a novel receptor for.alpha.4 integrins; US05580862 Sulfate ligands for L-selectins and methods ofpreventing sulfate addition; US05508387 Selectin binding glycopeptides; US06177547 Antibodies to P-selectin glycoprotein ligand; WO00079010A1 COMPOSITIONS AND METHODS FOR PREVENTINGTRANSEPITHELIAL TRANSMISSION OF HIV; US06096722 Antisense modulation of cell adhesion moleculeexpression and treatment of cell adhesion molecule-associateddiseases; US06030947 Methods of treating p150,95-mediatedinflammation and ICAM-1-mediated viral infection; US05948821 Methods of using ajoene; US05883082 Compositions and methods for preventing andtreating allograft rejection; US05874233 Methods of diagnosing a clinical subtype ofCrohn's disease with features of ulcerative colitis; 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EP00668871A1 AMINO-ACID SEQUENCE HOMOLOGIES BETWEENSELECTINS AND B. PERTUSSIS TOXIN-PEPTIDESDERIVED THERFROM, ANTIBODIES THERETO AND PHARMACEUTICAL COMPOSITIONS; EP00666914A1 NOVEL P-SELECTIN LIGAND PROTEIN; EP00642356A1 ANTIBODIES TO P-SELECTIN AND THEIR USES; US05395929 Isolated nucleic acid encoding the alphasubunit of the human leukocyte adhesion receptor; EP00314863B1 Use of ICAM-1 or its functional derivatives for the treatment of non-specific inflammation; US05367056 Endothelial cell-leukocyte adhesion molecules (ELAMs) and

molecules involved in leukocyte adhesion (MILAs); US05304640 DNA sequence encoding a selectin ligand; EP00584229A1 GLYCAM-1 (Sgp 50), A SELECTIN LIGAND; EP00544815A1 Peptides from the GMP-140 lectin binding domainand selectin binding ligandson carbonhydrates; US06193979 Compositions comprising complement receptortype 1 molecules having carbohydrate structures that are selectinligands; EP01037653A1 COMPOSITIONS AND METHODS FOR REGULATING PHAGOCYTOSIS AND ICAM-1 EXPRESSION; US06106834 Use of anti-CD45 leukocyte antigen antibodies for immunomodulation; EP01026250A1 DNA-constructs of blood clotting factors andP-selectin; US06100383 Fusion proteins comprising ICAM-R polypeptides and immunoglobulin constant regions; US06099838 Pharmaceutical compositions comprising anti-CD45RB antibodies for the inhibition of T-cell mediated immune responses; US06090914 CTLA4/CD28Ig hybrid fusion proteins and uses thereof; US06090840 Peptidyl compounds having MMP and TNFinhibitory activity; EP00639224B1 LECTIN DOMAIN VARIANTS OF SELECTIN; EP01010762A1 DNA constructs of blood clotting factors andP-Selectin; EP00840606B1 DI- AND TRIVALENT SMALL MOLECULE SELECTININHIBITORS; WO00027420A1 COMPOSITIONS AND METHODS FOR TREATMENT OF CANCER; WO00025808A1 INHIBITION OF DIFFERENTIATION OF CYTOTOXICT-CELLS BY P-SELECTIN LIGAND (PSGL) ANTAGONISTS; US06040428 Porcine E-selectin; US06040176 Antibodies to ICAM-related protein; US06004565 Compositions and methods of using compositions with accelerated lymphocyte homing immunosuppressive properties; US05994311 Cell adhesion peptides for modifying theadhesion capacity of eukaryotic cells between each other; US05977318 CTLA4 receptor and uses thereof; US05976877 Proteins produced by human lymphocytes DNA sequence encoding these proteins and their pharmaceutical andbiological uses; US05968510 CTLA4 receptor and uses thereof; US05962422 Inhibition of selectin binding; US05958705 Cytoplasmic modulators of integrinregulation/signaling; JP11246396A2 IMMUNOPOTENTIATOR; US05939525 Methods of treating inflammation andcompositions therefor; US05929036 Ligand or GMP-140 selectin and methods of use thereof; EP00929670A1 P-SELECTIN LIGAND PROTEINS; US05925531 Human bone marrow endothelial cell line and methods of use thereof; US05916876 Peptide inhibitors of leukocyte adhesion; US05916803 Target cell-specific non-viral vectors for inserting genes into cells, pharmaceutical compositions comprising such vectors and their use; WO09930730A1 METHODS AND COMPOSITIONS FOR IMPROVING THESUCCESS OF CELL TRANSPLANTATIONIN A HOST; US05914112 Anti-CD18 antibodies in stroke; EP00902681A1 INHIBITION OF SELECTIN BINDING; US05885796 CTLA4 receptor and uses thereof; US05885579 CTLA4 receptor and uses thereof; US05880268 Modulators of the interaction between ICAM-R and .alpha.d /CD18; US05879712 Method for producing drug-loaded microparticlesand an ICAM-1 dosage form so produced; US05874548 Regioselective sulfation; US05874250 DNA encoding for a protein containing theextracellular domain of lymphocyte activation gene 3; US05869262 Method for monitoring an inflammatory disease state by detecting circulating ICAM-R; 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EP00840606A1 DI- AND TRIVALENT SMALL MOLECULE SELECTIN INHIBITORS; EP00833650A1 P-SELECTIN LIGANDS AND RELATED MOLECULES AND METHODS; EP00804235A1 ANTIBODIES TO P-SELECTIN AND THEIR USES; US05652343 Method for purification of L-selectin ligands; US05648458 Peptides and compounds that bind to ELAM-1; US05648344 Methods of treating inflammation using selection binding compounds; JP09183789A2 NEW SULFATED AND PHOSPHATED SUGAR DERIVATIVE,ITS PRODUCTION AND USE; US05646248 E-selection binding soluble lamp-1 polypeptide; EP00771795A1 New glycomimetics as Selectin antagonists and anti-imflammation pharmaceutical compositions; US05624909 Derivatives of triterpenoid acids as inhibitors of cell-adhesion molecules ELAM-1 (e-selectin) and LECAM-1 (l-selectin); EP00765172A1 CROSS-REACTING MONOCLONAL ANTIBODIES SPECIFIC FOR E-SELECTIN AND P-SELECTIN; US05616488 IL-5 targeted ribozymes; EP00762886A1 ICAM-1/LFA-1 SHORT-CHAIN PEPTIDES AND METHOD OF USING SAME; US05595737 Methods for using monoclonal antibodies specific for cell-surface bound LAM-1; WO09701335A1 DI- AND TRIVALENT SMALL MOLECULE SELECTIN INHIBITORS; EP00391088B1 Use of functional derivatives of the intercellular adhesion molecule ICAM-1 in anti-viral therapy; US05580756 B7IG fusion protein; US05521288 CD28IG fusion protein; US05519008 Derivatives of triterpenoid acids as inhibitors of cell-adhesion molecules ELAM-1 (E-selectin) and LECAM-1 (L-selectin); EP00379904B1 A soluble molecule related to but distinctfrom ICAM-1; US05489533 Isolated nucleic acid molecules encodingICAM-2; US05487112 Method and apparatus for time-resolved measurements of lymphocyte function and aggregate structure usingcomputer-automated microscopy; EP00691813A1 DERIVATIVES OF TRITERPENOID ACIDS AS INHIBITORS OF CELL-ADHESION MOLECULESELAM-1 (E-SELECTIN) AND LECAM-1 (L-SELECTIN); EP00689599A1 CHIMERIC L- AND P-SELECTIN BY EXCHANGE OFDOMAINS - USES THEREOF; EP00671951A1 HUMANIZED ANTIBODIES REACTIVE WITHL-SELECTIN; EP00668907A1 GLYCOPROTEIN LIGAND FOR P-SELECTIN AND METHODS OF USE THEREOF; US05434131 Chimeric CTLA4 receptor and methods for its use; EP00656904A1 PEPTIDE INHIBITORS OF SELECTIN BINDING; EP00652897A1 PEPTIDE INHIBITORS OF SELECTIN BINDING; EP00639224A1 LECTIN DOMAIN VARIANTS OF SELECTIN; US05389520 Specific detection of cell surface receptor leukocyte adhesion molecule-1; EP00608260A1 PEPTIDE INHIBITORS OF INFLAMMATION MEDIATED BY SELECTINS; US05324510 Use of antibodies to intercellular adhesionmolecule-1 (ICAM-1) in the treatment of asthma;

EP00602194A1 PEPTIDE INHIBITORS OF INFLAMMATION MEDIATED BY SELECTINS; US05318890 Assays for inhibitors of leukocyte adhesion; US05316913 Neutrophil LECAM-1 as indicator of neutrophilactivation; US05284931 Intercellular adhesion molecules, and their binding ligands; EP00488061A3 The MAC-1 binding site of ICAM-1; EP00488061A2 The MAC-1 binding site of ICAM-1; EP00391088A3 Use of functional derivatives of theintercellular adhesion molecule ICAM-1 in anti-viral therapy; EP00391088A2 Use of functional derivatives of the intercellular adhesion molecule ICAM-1 in anti-viral therapy; EP00379904A1 A soluble molecule related to but distinct from ICAM-1; US06194557 Nucleic acid molecules encoding Bap-1 proteins; US06183988 Leukocyte-specific protein and gene, andmethods of use thereof; US06177475 Methods of using integrin modulators for treatment of inflammation; US06174914 Method of inhibiting cytokine release from human ocular cells; US06156878 Ligand (ACT-4-L) to a receptor on the surfaceof activated CD4+ T-cells; US06136790 Carbohydrate mimetics having antiadhesiveproperties; US06133239 Carbohydrate ligands (myelorollin) that causeE-selectin dependent cell rolling and adhesion under dynamic flowsystem; US06132764 Targeted polymerized liposome diagnostic and treatment agents; WO00060055A1 MODIFIED DENDRITIC CELLS AND USES THEREFOR; US06114517 Methods of modulating tumor necrosis factor .alpha.-induced expression of cell adhesion molecules; US06111093 CD19 coding sequences; US06111084 Fuopeptide mimetics; US06110922 Cell adhesion-inhibiting antiinflammatory and immune-suppressive compounds; US06110897 Antiinflammatory cell adhesion inhibitors; US06107365 Biomimetic hydrogel materials; US06107046 Antibodies to , a receptor tyrosine kinaseand uses thereof; WO00043023A1 PHARMACEUTICAL COMPOSITION WITH ADHESIONMOLECULE EXPRESSION REGULATING ACTIVITY; US06068829 Method of identifying molecules that home to a selected organ in vivo; US06066321 Method for antagonizing vascular adhesionprotein-1 (VAP-1)-mediated binding of endothelial cells to lymphocytes; US06063906 Antibodies to integrin alpha subunit; US06063585 TRAF inhibitors; US06060588 Bap-1 proteins; US06060303 TRAF inhibitors; US06060056 Composition for inducing humoral anergy to an immunogen comprising a T cell epitope-deficient analog of the immunogen conjugated to a nonimmunogenic valency platform molecule; US06057423 Integrin alpha subunit; US06051598 Amino ceramide-like compounds and therapeutic methods of use; US06051428 Rapid production of autologous tumor vaccines; US06046046 Compositions, methods and devices for maintaining an organ; US06043094 Therapeutic liposome composition and method; US06040332 Amino ceramide-like compounds and therapeutic methods of use; US06040147 Systemic inflammatory markers as diagnostic tools in the prevention of atherosclerotic diseases and as tools to aid in the selection of agents to be used for the prevention andtreatment of atherosclerotic disease; US06034238 Heterocyclic compounds, their preparation and their use as leucocyte adhesion inhibitors and VLA-4-antagonists; US05998598 Immunoadhesins and methods of production anduse thereof; US05997865 Agonist antibodies against the flk2/flt3 receptor and uses thereof; US05993816 Methods to inhibit humoral immune responses, immunoglobulin production and B cell activation with 5c8-specific antibodies; US05993800 Methods for prolonging the expression of aheterologous gene of interest using soluble CTLA4 molecules and an antiCD40 ligand; US05977303 Mammalian cell surface antigens; US05968755 Methods for determining T-cell profiles ofimmunocompromised subjects; EP00948597A1 HUMAN MUCOSAL ADDRESSIN CELL ADHESION MOLECULE-1 (MAdCAM-1) AND SPLICE VARIANTS THEREOF; US05955291 Antibodies recognizing tie receptor tyrosine kinase and uses thereof; US05932214 Treatment for inflammatory bowel disease with VLA-4 blockers; US05928643 Method of using CD2-binding domain of lymphocyte function associated antigen 3 to initiate T cell activation; US05922570 Cytoplasmic Modulators of Integrin Binding/Signalling; US05919768 Di- and trivalent small molecule selectin inhibitors; US05914111 CD2-binding domain of lymphocyte function associated antigen-3; US05904920 Regulation of systemic immune responsesutilizing cytokines and antigens; US05888969 Use of cytokine restraining agents to treat inflammatory bowel disease; US05876715 Antibodies that bind novel carbohydrate ligands (myelorollins) that cause E-selectin dependent cell rolling, anduses thereof; US05871734 Treatment for asthma with VLA-4 blocking agents; US05869619 Modified antibody variable domains; US05869453 Cytotoxic T-cell epitopes; US05861151 Soluble fusion molecules with binding specificity for cell adhesion molecules; US05851989 Method of extending the plasma half-life of vascular endothelial cell growth factor; US05843441 Use of endothelial-leukocyte adhesion molecule-1 specific antibodies in the treatment of asthma; WO09853049A1 VASCULAR ADHESION PROTEIN-1 HAVING AMINE OXIDASE ACTIVITY; JP10295375A2 SOLUBLE LFA-1 PROTEIN; US05831029 Human ࢸ integrin .alpha. subunit; US05821332 Receptor on the surface of activated CD4+ T-cells: ACT-4; US05821123 Modified antibody variable domains; EP00868197A1 ANTI-SELECTIN ANTIBODIES FOR PREVENTION OFMULTIPLE ORGAN FAILURE AND ACUTE ORGAN DAMAGE; US05817515 Human B2 integrin alpha subunit antibodies; WO09842750A1 ANTIGENIC FUSIONPROTEIN CARRYINGGAL.agr.1,3GAL EPITOPES; US05811300 TNF-.alpha. ribozymes; US05807745 Method of inhibiting PADGEM-mediated orELAM-1-mediated leukocyte adhesion using an inhibitor comprising aLex core component; US05792444 Labeled chemotactic peptides to image focal sites of infection or inflammation; EP00528931B1 HUMANIZED CHIMERIC ANTI-ICAM-1 ANTIBODIES, METHODS OF PREPARATION AND USE; US05776775 Anti-LAM 1-3 antibody and hybridoma; US05776755 FLT4, a receptor tyrosine kinase; US05766850 Human ࢸ integrin .alpha. subunit; US05766585 Systemic gene treatment of connective tissue diseases with IRAP-1; US05759855 Methods for modifying the binding activity of cell adhesion receptors; JP10130240A2 INHIBITOR OF ICAM-1-PRODUCTION; US05741667 Tumor necrosis factor receptor-associated factors; US05730983 Use of intercellular adhesion molecules, and their binding ligands in the treatment of asthma; US05730978 Inhibition of lymphocyte adherence with lpha.4ࢷ -specific antibodies; US05728533 Human ß2 integrin .alpha.subunit; US05693483 Cytoplasmic modulators of integrin binding/signalling; US05688656 Cytokine-induced marker for inflammatory response; JP09216902A2 NOVEL CARBOHYDRATE LIGAND (MYELOROLLIN) THAT CAUSES E-SELECTIN DEPENDENT CELL ROLLING AND ADHESION UNDER DYNAMIC FLOW SYSTEM; US05650396 Methods of modulating inflammatory cytokines in the CNS using TGF-ß; US05629412 Synthetic glycoamines that promote or inhibit cell adhesion; US06068829 Method of identifying molecules that home to a selected organ in vivo;

US06066321 Method for antagonizing vascular adhesion protein-1 (VAP-1)-mediated binding of endothelial cells tolymphocytes; US06063906 Antibodies to integrin alpha subunit; US06063585 TRAF inhibitors; US06060588 Bap-1 proteins; US06060303 TRAF inhibitors; US06060056 Composition for inducing humoral anergy to an immunogen comprising a T cell epitope-deficient analog of the immunogen conjugated to a nonimmunogenic valency platform molecule; US06057423 Integrin alpha subunit; US06051428 Rapid production of autologous tumor vaccines; US06043094 Therapeutic liposome composition and method; US06034238 Heterocyclic compounds, their preparation and their use as leucocyte adhesion inhibitors and VLA-4-antagonists; US05998598 Immunoadhesins and methods of production anduse thereof; US05997865 Agonist antibodies against the flk2/flt3 receptor and uses thereof; US05993816 Methods to inhibit humoral immune responses, immunoglobulin production and B cell activation with 5c8-specificantibodies; US05993800 Methods for prolonging the expression of a heterologous gene of interest using soluble CTLA4 molecules and an antiCD40 ligand; US05968755 Methods for determining T-cell profiles of immunocompromised subjects; EP00948597A1 HUMAN MUCOSAL ADDRESSIN CELL ADHESION MOLECULE-1 (MAdCAM-1) AND SPLICE VARIANTS THEREOF; recognizing tie receptor tyrosine kinase and uses thereof; US05951982 Methods to suppress an immune response with variant CD44-specific antibodies; US05932214 Treatment for inflammatory bowel disease with VLA-4 blockers; US05928643 Method of using CD2-binding domain of lymphocyte function associated antigen 3 to initiate T cellactivation; US05904920 Regulation of systemic immune responses utilizing cytokines and antigens; US05888978 Method for reducing the severity of gastro-intestinal damage; US05888969 Use of cytokine restraining agents to treat inflammatory bowel disease; US05876715 Antibodies that bind novel carbohydrate ligands(myelorollins) that cause E-selectin dependent cell rolling, anduses thereof; US05871734 Treatment for asthma with VLA-4 blocking agents; US05869619 Modified antibody variable domains; US05869453 Cytotoxic T-cell epitopes; US05861151 Soluble fusion molecules with binding pecificity for cell adhesion molecules; US05851989 Method of extending the plasma half-life ofvascular endot helial cell growth factor; US05843441 Use of endothelial-leukocyte adhesionmolecule-1 specific antibodies in the treatment of asthma; WO09853049A1 VASCULAR ADHESION PROTEIN-1 HAVING AMINE OXIDASE ACTIVITY; JP10295375A2 SOLUBLE LFA-1 PROTEIN; US05831029 Human ࢸ integrin .alpha. subunit; US05821332 Receptor on the surface of activated CD4+T-cells: ACT-4; US05821123 Modified antibody variable domains; EP00868197A1 ANTI-SELECTIN ANTIBODIES FOR PREVENTION OF MULTIPLE ORGAN FAILURE AND ACUTE ORGAN DAMAGE; US05817515 Human B2 integrin alpha subunit antibodies; US05807745 Method of inhibiting PADGEM-mediated or ELAM-1-mediated leukocyte adhesion using an inhibitor comprising a Lex core component; EP00528931B1 HUMANIZED CHIMERIC ANTI-ICAM-1 ANTIBODIES, METHODS OF PREPARATION AND USE; US05776775 Anti-LAM 1-3 antibody and hybridoma; US05776755 FLT4, a receptor tyrosine kinase; US05770196 Modified antibody variable domains and therapeutic uses thereof; US05766886 Modified antibody variable domains; US05766854 Method for identifying active domains and amino acid residues in polypeptides and hormone variants; US05759855 Methods for modifying the binding activity of cell adhesion receptors; US05741667 Tumor necrosis factor receptor-associated factors; US05730983 Use of intercellular adhesion molecules, andtheir binding ligands in the treatment of asthma; US05730978 Inhibition of lymphocyte adherence with alpha.4ࢷ -specific antibodies; US05728533 Human ß2 integrin .alpha.subunit; US05693483 Cytoplasmic modulators of integrin binding/signalling; US05688656 Cytokine-induced marker for inflammatory response; JP09216902A2 NOVEL CARBOHYDRATE LIGAND (MYELOROLLIN) THAT CAUSES E-SELECTIN DEPENDENT CELL ROLLING AND ADHESION UNDER DYNAMICFLOW SYSTEM; US05650396Methods of modulating inflammatory cytokines inthe CNS using TGF-ß; US05648465Cloning and expression of neurocan, achondroitin sulfate proteoglycan; US05646250 Cadherin polypeptides; US05646123 Time dependent administration ofoligosaccharide glycosides related to blood group determinants having a type I or type II core structure in reducing inflammation in a sensitized mammal arising form exposure to an antigen; US05629412Synthetic glycoamines that promote or inhibit cell adhesion.Examples of tumor specific antigens are numerous and are referred to in the hereinabove cited references andas well as the in the following references. US06083703O7/04/2000 Identification of TRP-2 as a human tumor antigen recognized by cytotoxic T lymphocytesUS06132980l0/17/2000 Antibodies specific for TRP-2 a human tumor antigen recognized by cytotoxic T lymphocytes; US05831016l1/03/1998 Identification of TRP-2 as a human tumor antigen recognized by cytotoxic T lymphocytes; US05932210l2/03/1999 Recombinant adenoviral vector and methods of use; US05907078O5/25/1999 Transgenic mouse model for prostate cancerUS05693522l2/02/1997 Anti-cancer immunotherapeutics US05635473 06/03/1997 Inhibitor of hepatitis B virus replicationUS06087110O7/11/2000 Alternative open reading frame DNA of a normalgene and a novel human cancer antigen encoded therein US06074650O6/13/2000 Membrane anchor/active compound conjugate, itspreparation and its uses US05766588O6/16/1998 Tumor immunotherapy using anti-idiotypicantibodiesUS05756349O5/26/1998 Production of erythropoietin US05614610O3/25/1997 Tumor immunotherapy using anti-idiotypic antibodies US05354847l0/11/1994 Chimeric antibody with specificity to humantumor antigenUS05306811O4/26/1994 Squamous cell carcinoma-like immunoreactiveantigen from human female urineUS05208146O5/04/1993 Murine monoclonal anti-idiotype antibodiesUS04918164O4/17/1990 Tumor immunotherapy using anti-idiotypicantibodiesUS04403040O9/06/1983 Diagnostic test for the detection of a specifictumor antigen with CoA-SPCUS06165464l2/26/2000 Monoclonal antibodies directed to the HER2receptorUS06156305l2/05/2000 Implanted tumor cells for the prevention and treatment of cancer; US06096520 08/01/2000 Brain glycogen phosphorylase cancer antigenUS06054561O4/25/2000 Antigen-binding sites of antibody moleculesspecific for cancer antigensUS06024964O2/15/2000 Membrane anchor/active compound conjugate, itspreparation and its usesUS06004548l2/21/1999 Analogs of pluripotent granulocytecolony-stimulating factorUS05951975O9/14/1999 Induction of CTLs specific for natural antigensby cross priming immunizationUS05877305O3/02/1999 DNA encoding biosynthetic binding protein forcancer markerUS05840839l1/24/1998 Alternative open reading frame DNA of a normalgene and a novel human cancer antigen encoded thereinUS05830705l1/03/1998 Method for recombinant production of humanpluripotent

granulocyte colony-stimulating factorUS0582431110/20/1998 Treatment of tumors with monoclonal antibodiesagainst oncogene antigensUS0580798909/15/1998 Methods for treatment or diagnosis of diseasesor disorders associated with an APB domainUS0578896308/04/1998 Isolation and/or preservation of dendriticcells for prostate cancer immunotherapyUS0567694110/14/1997 Methods of enhancing bone marrowtransplantation and treating burn wounds comprising administeringhuman pluripotent granulocyte colony-stimulating factorUS0566290709/02/1997 Induction of anti-tumor cytotoxic T lymphocytesin humans using synthetic peptide epitopesUS0553222007/02/1996 Genetic mechanisms of tumor suppressionUS0552767606/18/1996 Detection of loss of the wild-type P53 gene andkits thereforUS0549683103/05/1996 Inhibition of insulin-induced adiposisUS0524867109/28/1993 Methods and compositions for treatment ofcancer using oligonucleotidesUS0484950907/18/1989 Monoclonal antibodies againstmelanoma-associated antigens and hybrid cell lines producing theseantibodiesUS0459155205/27/1986 Detection of hepatitis B surface antigen (orantibody to same) with labeled synthetic peptideUS0458427804/22/1986 Antigen derived from human ovarian tumors andradioimmunoassay using the antigenUS0404375708/23/1977 Method for detection of human mammarycarcinomaUS0619775403/06/2001 Suppression of tumor growth by a mini-E1AgeneUS0618730702/13/2001 Cancer immunotherapy with semi-allogeneiccellsUS0618374602/06/2001 Immunogenic peptides from the HPV E7 proteinUS0618061201/30/2001 Methods and compositions for targeting DNAmetabolic processes using aminoglycoside derivativesUS0617726701/23/2001 Acetyl-CoA carboxylase from wheatUS0614687711/14/2000 Identification of the progression elevatedgene-3 and uses thereofUS0614329711/07/2000 Methods of promoting immunopotentiation andpreparing antibodies with anti-CD3 antibodiesUS0614012610/31/2000 Antisense modulation of Y-box binding protein 1expressionUS0614005810/31/2000 Activation of p53 proteinUS0614005010/31/2000 Methods for determining breast cancer andmelanoma by assaying for a plurality of antigens associatedtherewithUS0613658010/24/2000 ß-1-6-N-acetylglucosaminyltransferase thatforms core 2, core 4 and I branchesUS0613271810/17/2000 Multi-stage cascade boosting vaccineUS0611390109/05/2000 Methods of stimulating or enhancing the immunesystem with anti-CD3 antibodiesUS0611074408/29/2000 Diminishing viral gene expression by promoterreplacementUS0611074308/29/2000 Development and use of human pancreatic celllinesUS0610747408/22/2000 Nucleotide sequence encoding a 14 kDa proteinfrom goat liverUS0609078907/18/2000 Synthesis of the breast tumor-associatedantigen defined by monoclonal antibody MBr1 and uses thereofUS0608744107/11/2000 Structurally modified peptides that areresistant to peptidase degradationUS0608717107/11/2000 Method for inducing DNA synthesis in neuronsUS0608408507/04/2000 Inducing resistance to tumor growth withsoluble IGF-1 receptorUS0608040906/27/2000 Immunostimulatory methodUS0608039906/27/2000 Vaccine adjuvants for immunotherapy ofmelanomaUS0607795006/20/2000 Methods for enhancing an immune response from a43 KD human cancer antigenUS0606923105/30/2000 PR domain peptidesUS0606390005/16/2000 Isolated tumor rejection antigen precursorMAGE-2 derived peptides, and uses thereofUS0606337905/16/2000 Anti-idiotypic monoclonal antibodies andcompositions including the anti-idiotypic monoclonal antibodiesUS0606023805/09/2000 Method and composition for regulatingapoptosisUS0605446704/25/2000 Down-regulation of DNA repair to enhancesensitivity to P53-mediated apoptosisUS0605169304/18/2000 CLNH11-specific antibodiesUS0605139604/18/2000 Method for producing retinoblastoma geneprotein productsUS0605138704/18/2000 Methods of determining the presence of aneoplasm with CLNH5- and CLNH11-specific antibodiesUS0605122904/18/2000 Human-human hybridom for neoplasms CLNH5 andCLNH11 specific antibody compositionsUS0605122604/18/2000 MN-specific antibodies and their use in cancertreatmentUS0604600704/04/2000 Method and composition for regulatingapoptosisUS0603713403/14/2000 Methods that detect compounds that disruptreceptor tyrosine kinase/GRB-7 complexesUS0603421403/07/2000 Isolated nonapeptides which bind to HLAmolecules and provoke lysis by cytolytic T cellsUS0602792402/22/2000 Isolated nucleic acid molecule coding for tumorrejection antigen precursor MAGE-C1 and uses thereofUS0602791602/22/2000 Galectin 9 and 10SV PolynucleotidesUS0602547402/15/2000 Isolated nucleic acid molecules coding fortumor rejection antigen precursor mage-3 and uses thereofUS0602295802/08/2000 cDNAs coding for members of thecarcinoembryonic antigen familyUS0602269202/08/2000 Method for screening for possible presence ofcancerUS0602014502/01/2000 Methods for determining the presence ofcarcinoma using the antigen binding region of monoclonal antibodyBR96US0601998702/01/2000 Isolated, MAGE-3 derived peptides which complexwith HLA-A2 molecules and uses thereofUS0601754001/25/2000 Prevention and treatment of primary andmetastatic neoplastic diseases and infectious diseases with heatshock/stress protein-peptide complexesUS0601566501/18/2000 Method and composition for regulatingapoptosisUS0601556701/18/2000 HER2 extracellular domainUS0601377201/11/2000 Antibody preparations specifically binding tounique determinants of CEA antigens or fragments thereof and use ofthe antibody preparations in immunoassaysUS0601348101/11/2000 Isolated, nucleic acid molecules which code forgage tumor rejection antigen, the tumor rejection antigen, and usesthereofUS0601325801/11/2000 Immunogenic peptides from the HPV E7 proteinUS0600799112/28/1999 Antisense oligonucleotides formitogen-activated protein kinases as therapy for cancerUS0600158312/14/1999 Methods for disrupting GRB-7 complexesUS0599820512/07/1999 Vectors for tissue-specific replicationUS0599412611/30/1999 Method for in vitro proliferation of dendriticcell precursors and their use to produce immunogensUS0599406211/30/1999 Epithelial protein and DNA thereof for use inearly cancer detectionUS0598527011/16/1999 Adoptive immunotherapy using macrophagessensitized with heat shock protein-epitope complexesUS0598157511/09/1999 Inhibition of fatty acid synthase as a means toreduce adipocyte massUS0598089611/09/1999 Antibodies reactive with human carcinomasUS0595527509/21/1999 Methods for identifying nucleic acid sequencesencoding agents that affect cellular phenotypesUS0595507509/21/1999 Method of inhibiting tumor growth usingantibodies to MN proteinUS0595248809/14/1999 Androgen regulation with DNA sequences of ratprobasin geneUS0593242108/03/1999 Methods and cell lines for identification ofregulators of integrin

activationUS0591976407/06/1999 Compounds that bind to p185 and methods ofusing the sameUS0591712406/29/1999 Transgenic mouse model of prostate cancerUS0591438906/22/1999 E6 associated proteinUS0591214306/15/1999 Polynucleotides encoding a human mage proteinhomologUS0591062606/08/1999 Acetyl-CoA carboxylase compositions and methodsof useUS0587456002/23/1999 Melanoma antigens and their use in diagnosticand therapeutic methodsUS0587221702/16/1999 Antibodies which specifically bind a cancerrelated antigenUS0586963602/09/1999 Immunoreactive peptide sequence from a 43 kDhuman cancer antigenUS0586904502/09/1999 Antibody conjugates reactive with humancarcinomasUS0586612402/02/1999 Antiidiotypic antibodies for high molecularweight-melanoma associated antigenUS0586401101/26/1999 Cancer related antigenUS0586138101/19/1999 Pharmaceutical composition for the treatment ofa malignant tumorUS0585611201/05/1999 Method for selectively inducing biomarkerexpression in urologic tumor tissue for diagnosis and treatmentthereofUS0585609101/05/1999 Isolated nucleic acid sequence coding for atumor rejection antigen precursor processed to at least one tumorrejection antigen presented by HLA-A2US0585199112/22/1998 Therapeutic use of the retinoblastomasusceptibility gene productUS0585176412/22/1998 Human prostate tumor inducing gene-1 and usesthereofUS0585152312/22/1998 Isolated, peptides derived from MAGE tumorrejection antigen precursors which complex with HLA-A2 molecules anduses thereofUS0584951712/15/1998 Method and composition for preserving antigensand nucleic acids and process for utilizing cytological materialproduced by sameUS0584708312/08/1998 Modified p53 constructs which enhance DNAbindingUS0584407512/01/1998 Melanoma antigens and their use in diagnosticand therapeutic methodsUS0584368512/01/1998 Production of chimeric mouse-human antibodieswith specificity to human tumor antigensUS0584364812/01/1998 P15 and tyrosinase melanoma antigens and theiruse in diagnostic and therapeutic methodsUS0584085411/24/1998 Monoclonal antibody BR110 and uses thereofUS0583784611/17/1998 Biosynthetic binding proteins forimmuno-targetingUS0583723111/17/1998 GM-CSF administration for the treatment andprevention of recurrence of brain tumorsUS0583100811/03/1998 Retinoblastoma protein-interacting zinc fingerproteinsUS0583047011/03/1998 Humanized antibodies to ganglioside GM2US0583046411/03/1998 Compositions and methods for the treatment andgrowth inhibition of cancer using heat shock/stress protein-peptidecomplexes in combination with adoptive immunotherapyUS0582766610/27/1998 Synthetic multiple tandem repeat mucin andmucin-like peptides, and uses thereofUS0582465810/20/1998 Topical composition containing hyaluronic acidand NSAIDSUS0582107010/13/1998 Antibodies reactive with retinoblastoma bindingproteins and methods of using sameUS0581751310/06/1998 Anti ganglioside monoclonal antibodiesUS0581130409/22/1998 Nucleic acid molecules encoding retinoblastomaprotein-interacting zinc finger proteinsUS0581109909/22/1998 Method and composition for preserving antigensand process for utilizing cytological material produced by sameUS0580800509/15/1998 Human carcinoma antigenUS0580123309/01/1998 Nucleic acid compositions encoding acetyl-coaacarboxylase and uses thereforUS0579822908/25/1998 Bispecific molecules recognizing lymphocyteantigen CD2 and tumor antigensUS0579809008/25/1998 Enhancement of the cellular immune responseUS0579245608/11/1998 Mutant BR96 antibodies reactive with humancarcinomasUS0578368107/21/1998 Androgen regulation with DNA sequences of ratprobasin geneUS0577357906/30/1998 Lung cancer markerUS0577299706/30/1998 Monoclonal antibodies directed to the HER2receptorUS0577037406/23/1998 Methods for identifying oncogenes andanti-oncogenesUS0577019506/23/1998 Monoclonal antibodies directed to the her2receptorUS0576691006/16/1998 Expression of the developmental I antigen by acloned human cDNA encoding a member of a beta-1,6-N-acetylglucosaminyltransfrase gene familyUS0576657106/16/1998 Method of treating human breast cancer byadministration of radiolabeled antibody and unsaturated fattyacidsUS0576322406/09/1998 Decay accelerating factor (DAF) and nucleicacids encoding itUS0575983706/02/1998 Chemotherapy for cancer by inhibiting the fattyacid biosynthetic pathwayUS0575979106/02/1998 Cancer related antigenUS0575326005/19/1998 Vaccines against sterolsUS0575320405/19/1998 Biosynthetic binding proteins forimmunotargetingUS0575039505/12/1998 DNA encoding MAGE-1 C-terminal cytotoxic tlymphocyte immunogenic peptidesUS0574765005/05/1998 P53AS protein and antibody thereforUS0574726805/05/1998 Tumor marker controlUS0574707205/05/1998 Adenoviral-mediated gene transfer to synovialcells in vivoUS0574414404/28/1998 Synthetic multiple tandem repeat mucin andmucin-like peptides, and uses thereofUS0574164804/21/1998 Cell analysis method using quantitativefluorescence image analysisUS0573372103/31/1998 Cell analysis method using quantitativefluorescence image analysisUS0573142003/24/1998 Antibodies to human I-branchingbeta-1,6-N-acetylglucosaminyltransferaseUS0572882103/17/1998 Mutant BR96 antibodies reactive with humanoarcinomasUS0572585603/10/1998 Monoclonal antibodies directed to the HER2receptorUS0572333303/03/1998 Human pancreatic cell lines: developments andusesUS0572134002/24/1998 p53 proteins with altered tetramerizationdomainsUS0572095402/24/1998 Monoclonal antibodies directed to the HER2receptorUS0572093702/24/1998 In vivo tumor detection assayUS0571417002/03/1998 Method of inducing resistance to tumor growthUS0570515701/06/1998 Methods of immunoreactive peptide sequence from a 43 KDhuman cancer antigenUS0569599412/09/1997 Isolated cytolytic T cells specific treating cancerous cells withanti-receptor antibodiesUS0569376312/02/1997 Antibodies to human forcomplexes of MAGE related peptides and HLA moleculesUS0569361712/02/1997 Inhibitors of the 26s proteolytic complex andthe 20s proteasome carcinoma antigenUS0569351112/02/1997 Immortalized human fetal osteoblastic cellsUS0569117511/25/1997 contained thereinUS0568848811/18/1997 Composition and method for tumor imaging Immortalized human fetal osteoblastic cellsUS0568606811/11/1997 Isolated peptides derived from MAGE-2,cytolytic T cells specific to complexes of peptide and HLA-A2molecules, and uses thereofUS0568413411/04/1997 Antibody specific for ࢷ .fwdarw.6N-acetylglucosamininyltransferaseUS0568388611/04/1997 Tumor rejection antigens which correspond toamino acid sequences in tumor rejection antigen precursor bage, anduses thereofUS0568170110/28/1997 Immortalized human fetal osteoblastic cellsUS0568156210/28/1997 Lymphokine gene therapy of

cancerUS0567717110/14/1997 Monoclonal antibodies directed to the HER2receptorUS0567448610/07/1997 Cancer immunotherapy with carrier cellsUS0566587409/09/1997 Cancer related antigenUS0566535709/09/1997 Antibodies recognizing tumor associated antigen CA 55.1 US0563144 09/02/1997 Compounds that bind to p185 and methods ofusing the same US0565877808/19/1997 ࢷ -6 N-acetylglucosaminyl, transferase, itsacceptor molecule, leukosialin, and a method for cloning protein shaving enzymatic activity US0565877408/19/1997 IRF-1 DNA expression inhibits growth of cellsexpressing c-myc or FosBUS0564822607/15/1997 Isolated peptides derived from tumor rejectionantigens, and their useUS0564583507/08/1997 Therapeutic antibody based fusion proteinsUS0563314205/27/1997 WT1 monoclonal antibodies and methods of usethereforUS0562483204/29/1997 ࢷ 6 N-acetylglucosaminyltransferase, itsacceptor molecule, leukosialin, and a method for cloning proteinshaving enzymatic activityUS0562482004/29/1997 Episomal expression vector for human genetherapyUS0562283604/22/1997 Monoclonal antibodies which recognize malignantcells from bladder carcinomasUS0562088604/15/1997 Isolated nucleic acid sequence coding for atumor rejection antigen precursor processed to at least one tumorrejection antigen presented by HLA-A2US0561001303/11/1997 Method for diagnosing a disorder by determiningexpression of gage tumor rejection antigen precursors US0559143001/07/1997 Isolated, MAGE-3 derived peptides which complexwith HLA-A2 molecules and uses thereofUS0558957912/31/1996 Gene sequence and probe for a marker ofnon-small cell lung carinomaUS0557392511/12/1996 P53 proteins with altered tetramerizationdomainsUS0557171111/05/1996 Isolated nucleic acid molecules coding for BAGEtumor rejection antigen precursorsUS0556554810/15/1996 Pre-S gene coded peptide hepatitis B immunogensand synthetic lipid vesicle carriersUS0555472409/10/1996 Isolated tumor rejection antigen precursorMAGE-2 derived peptides, and uses thereofUS0555450609/10/1996 Isolated, MAGE-3 derived peptides which complexwith HLA-A2 molecules and uses thereofUS0555229309/03/1996 Tumor antigen specific antibodyUS0554553208/13/1996 Human carcinoma antigen (HCA), HCA antibodies,HCA immunoassays and methods of imagingUS0553425407/09/1996 Biosynthetic binding proteins forimmuno-targetingUS0553234807/02/1996 E6 associated protein and methods of usethereofUS0552128505/28/1996 CTAA 28A32, the antigen recognized by MCA28A32US0549500202/27/1996 Tumor associated monoclonal antibody 123AV16US0548952502/06/1996 Monoclonal antibodies to prostate cellsUS0548645601/23/1996 Method of diagnosing ovarian, endometrial, andcolon cancers with monoclonal antibodies OXA and OXBUS0548459001/16/1996 Expression of the developmental I antigen by acloned human cDNA encoding a member of aß-1,6-N-acetylglucosaminyltransferase gene familyUS0547475512/12/1995 Tumor associated monoclonal antibodiesUS0546079710/24/1995 Method for fixing tissues and cells foranalysis using oxazolidine compoundsUS0545907310/17/1995 Method and composition for preserving antigensand process for utilizing cytological material produced by sameUS0541188405/02/1995 Monoclonal antibody L53 which recognizes a human tumor-associated antigenUS0537454812/20/1994 Methods and compositions for the attachment ofproteins to liposomes using a glycophospholipid anchorUS0535903110/25/1994 Unique protein marker for bladder cancerUS0533883208/16/1994 Antigen recognized by MCA 16-88US0522715907/13/1993 Anti-idiotype antibodies reactive with sharedidiotopes expressed by B cell lymphomas and autoantibodiesUS0522161206/22/1993 Unique protein marker for bladder cancerUS0521786406/08/1993 Replication initiator protein complex andmethods of use thereofUS0520409604/20/1993 Pre-S gene coded peptide hepatitis Bimmunogens, vaccines, diagnostics, and synthetic lipid vesiclecarriersUS0520050804/06/1993 Cell surface antigen that binds with L6monoclonal antibodyUS0519253703/09/1993 Method of treating renal cell carcinoma usingactivated mononuclear cells, renal tumor antigen and cimetidineUS0517166512/15/1992 Monoclonal antibody to novel antigen associatedwith human tumorsUS0513407507/28/1992 Monoclonal antibody to novel antigen associatedwith human tumorsUS0503961108/13/1991 Monoclonal antibodies to superficial papillarybladder tumor cellsUS0502655706/25/1991 Adjuvant compositionUS0501938305/28/1991 Fatty acid carriers for synthetic peptidesUS0501664405/21/1991 Urine testing module and method of collectingurine antigenUS0500304603/26/1991 Monoclonal antibody producing hybridoma andcorresponding antibody specific for human breast fibroblast tumorantigenUS0496071610/02/1990 Monoclonal antibodies specific for 330 KDbreast tumor antigen and assay using said monoclonal antibodiesUS0495932009/25/1990 Monoclonal antibody, process for preparingsame, reagent for detecting cancer antigen containing the monoclonalantibody and process for preparing sameUS0492179005/01/1990 Tumor specific assay for CA125 ovarian cancerantigenUS0484708007/11/1989 Pre-S gene coded peptide hepatitis Bimmunogens, vaccines, diagnostics, and synthetic lipide vesiclecarriersUS0482899105/09/1989 Tumor specific monoclonal antibodiesUS0474354305/10/1988 Method for enhancing and/or acceleratingimmunoassay detection of human carcinoma tumor associated antigen ina pathology sampleUS0469100909/01/1987 Hybrid proteins produced by an ultrahighprokaryotic expression systemUS0468320007/28/1987 Monoclonal antibody to human cancer antigen andmethod for producing sameUS0467038606/02/1987 Cancer tests using tumor antigen generatedlymphokines and compositionsUSRE03241705/12/1987 Radiolabeled antibody to anti-tumor associatedantigen and processUS0456216012/31/1985 Melanoma tumor antigen and autologousantibodyUS0455410111/19/1985 Identification and preparation of epitopes onantigens and allergens on the basis of hydrophilicityUS0447237109/18/1984 Radiolabeled antibody to anti-tumor associatedantigen and processUS0440159208/30/1983 Pharmaceutical composition having antitumoractivityUS0431585102/16/1982 Pharmaceutical composition having antitumoractivityUS0424366301/06/1981 Glycolipid compositions for transplanted tumorimmunotherapyUS0413276901/02/1979 Cancer antigen, cancer therapy, and cancerdiagnosis JP01044856A202/17/1989 ANTI-CANCER ANTIGEN ANTI-SERUMWO00006595A102/10/2000 HLA-A2 RESTRAINT TUMOR ANTIGEN PEPTIDEORIGINATING IN SART-1WO09940837A208/19/1999 COMPOSITIONS FOR DETECTING AND SURGICALLYREMOVING LYMPHOID TISSUE INVOLVED IN TUMOR PROGRESSIONWO00032770A106/08/2000 NOVEL TUMOR ANTIGEN PROTEIN ART-1 AND TUMORANTIGEN PEPTIDE THEREOFWO00012701A103/09/2000 NOVEL TUMOR ANTIGEN PROTEIN SART-3 AND

TUMORANTIGEN PEPTIDE THEREOFJP63012963A201/20/1988 CANCER ANTIGENJP62163686A207/20/1987 METHOD FOR ESTABLISHING ANTIBODY-FORMING CELLSTRAINJP62012718A201/21/1987 LABELED T-CELL ANTIGEN RECEPTOREP00974653A201/26/2000 Human gastric cancer antigen gene andproteinWO09967288A112/29/1999 TUMOR ANTIGEN PEPTIDES ORIGINATING INCYCLOPHILIN BWO09942140A108/26/1999 DETECTOR MOLECULE FOR USE IN A METHOD FORDETECTING AND SURGICALLY REMOVING LYMPHOID TISSUE INVOLVED IN TUMORPROGRESSIONWO09746676A112/11/1997 TUMOR ANTIGEN PROTEINS, GENES THEREOF, ANDTUMOR ANTIGEN PEPTIDESWO09735008A109/25/1997 METHODS AND COMPOSITIONS OF CHIMERICPOLYPEPTIDES FOR TUMOR ANTIGEN VACCINESJP63047664A202/29/1988 METHOD FOR MEASURING CANCER ANTIGEN AND KITTHEREFORJP62238464A210/19/1987 QUANTIFICATION OF HUMAN LUNG CANCER ANTIGENEP01055684A111/29/2000 TUMOR ANTIGEN PEPTIDE DERIVATIVESEP01041146A110/04/2000 TUMOR ANTIGEN PROTEIN, GENE THEREOF, ANDUTILIZATION THEREOFWO00052165A209/08/2000 COMPOSITIONS AND METHODS FOR BREAST CANCERTHERAPY AND DIAGNOSISJP00184880A207/04/2000 PROPAGATION AND ACTIVATING INDUCTION OFCYTOTOXIC T-CELL SPECIFIC TO CANCER CELL AND DEVICE THEREFORJP00116383A204/25/2000 HUMAN CANCER REGRESSION ANTIGEN PROTEINWO00002907A101/20/2000 TUMOR ANTIGEN PEPTIDE ORIGINATING IN SART-1WO09933977A107/08/1999 TUMOR ANTIGEN PROTEIN, GENE THEREOF, ANDUTILIZATION THEREOFWO09929715A106/17/1999 TUMOR ANTIGEN PEPTIDE DERIVATIVESWO09918206A204/15/1999 NOVEL HUMAN CANCER ANTIGEN NY ESO-1/CAG-3 ANDGENE ENCODING SAMEWO09906834A202/11/1999 METHODS FOR IDENTIFYING LIGAND SPECIFICBINDING MOLECULESWO09804282A102/05/1998 CANCER IMMUNOTHERAPY USING AUTOLOGOUS TUMORCELLS COMBINED WITH ALLOGENEICCYTOKINE-SECRETING CELLSJP07089873A204/04/1995 BISPECIFIC TRIGGER MOLECULE RECOGNIZINGLYMPHOCYTE ANTIGEN CD2 AND TUMOR ANTIGENJP63041427A202/22/1988 HUMAN CANCER ANTIGENJP61216683A209/26/1986 B-LYMPHOCYTE STRAIN ORIGINATED FROM BLOOMSYNDROME PATIENT HAVING COMMON CANCER ANTIGENWO00111044A102/15/2001 TUMOR ANTIGENWO00054807A109/21/2000 LIGAND-BONDED COMPLEXWO00030680A106/02/2000 TUMOR ANTIGEN-SPECIFIC ANTIBODY-GP39 CHIMERICPROTEIN CONSTRUCTSJP00000092A201/07/2000 ANTI-HUMAN BREAST CANCER MONOCLONALANTIBODYWO00000591A101/06/2000 HUMAN MONOCLONAL ANTIBODIES AGAINST THE TUMORANTIGEN UK114 AND LYMPHOCYTE CELLS AND HYBRIDOMAS FOR THEIRPRODUCTIONWO09943857A109/02/1999 DETECTION OF METASTATIC CANCER CELLS USINGPCTA-1WO09936094A207/22/1999 COMPOSITION AND METHOD FOR TREATINGMETASTATIC TUMORS OR CANCER INDUCED BY CELLS EXPRESSING SV40 TUMORANTIGENJP11160318A206/18/1999 DETECTION AND DIAGNOSIS METHODS OF TUMORANTIGEN OF SMALL ANIMALJP11118805A204/30/1999 MEASURING VESSEL, MEASURING KIT ANDMEASUREMENT METHOD OF CANCER-ANTIGEN SPECIFIC CELLULARIMMUNO-RESPONSEEP00911397A104/28/1999 TUMOR ANTIGEN PROTEINS, GENES THEREOF, ANDTUMOR ANTIGEN PEPTIDESWO09822825A205/28/1998 A WHOLE BLOOD/MITOGEN ASSAY FOR THE EARLYDETECTION OF A SUBJECT WITH CANCER AND KITWO09822582A105/28/1998 HUMAN CANCER REGRESSION ANTIGEN PROTEINWO09729195A208/14/1997 HUMAN CANCER ANTIGEN OF TYROSINASE-RELATEDPROTEIN 1 AND 2 AND GENES ENCODING SAMEJP09151200A206/10/1997 PEPTIDE CAPABLE OF INDUCING IMMUNE RESPONSETO HUMAN GASTRIC CANCER, THERAPEUTIC AND PREVENTIVE AGENT FOR HUMANGASTRIC CANCER CONTAINING THE SAMEWO09704802A102/13/1997 ISOLATION AND/OR PRESERVATION OF DENDRITICCELLS FOR PROSTATE CANCER IMMUNOTHERAPYJP08308126A211/04/1994 DEVICE AND METHOD FOR EXAMINING MOLECULARSPECIMEN IN BIOLOGICAL FLUID AND COLLECTING CELL COMPONENTJP02172923A207/04/1990 METHOD FOR TREATING CANCERJP01163130A206/27/1989 VACCINE CONTAINING TUMOR ANTIGEN ANDADJUVANTJP01045397A202/17/1989 CANCER ANTIGENJP61277635A212/08/1986 DIAGNOSTIC AGENTJP61234358A210/18/1986 ASSAY OF HUMAN LUNG CANCER ANTIGENJP56065829A206/03/1981 ANTITUMOR AGENTJP56065828A206/03/1981 ANTITUMOR AGENTEP01072272A101/31/2001 METHOD FOR PRODUCING A SPECIFIC ANTISERUMAGAINST THE UNIVERSAL TUMOROUS ANTIGEN AND METHOD FOR DIAGNOSINGMALIGNANT TUMOURS USING SAID ANTISERUMEP01062335A112/27/2000 BREAST CANCER ANTIGENWO00052463A109/08/2000 METHOD OF DIAGNOSING AND MONITORING MALIGNANTBREAST CARCINOMASWO00047228A108/17/2000 METHODS FOR TREATMENT OF TUMORS ANDMETASTASES USING A COMBINATION OF ANTI-ANGIOGENIC AND IMMUNOTHERAPIESWO00044782A208/03/2000 EWING'S TUMOUR ANTIGEN, NUCLEIC ACID ANDANTIBODIESEP01021535A207/26/2000 HUMAN CANCER ANTIGEN NY-ESO-1/CAG-3 AND GENEENCODING SAMEWO00026676A105/11/2000 CANCER-ASSOCIATED ANTIGENS AND METHODS OFTHEIR IDENTIFICATIONWO00024778A105/04/2000 HLA-A2 AND HLA-DR SPECIFIC PEPTIDE EPITOPESFROM THE MELANOMA ANTIGEN TRP2WO00020460A104/13/2000 METHODS FOR PRODUCING HUMAN TUMOR ANTIGENSPECIFIC ANTIBODIESJP00072693A203/07/2000 MEDICINE TO BE INJECTED INTO SPLEENWO00009691A202/24/2000 BPC-1: A SECRETED BRAIN SPECIFIC PROTEINEXPRESSED AND SECRETED BY PROSTATE AND BLADDER CANCER CELLSWO09964590A112/16/1999 POLYMORPHIC MARKERS OF PROSTATE CARCINOMATUMOR ANTIGEN-1 (PCTA-1)WO09962942A212/09/1999 NOVEL TUMOR ANTIGEN USEFUL IN DIAGNOSIS ANDTHERAPY OF PROSTATE AND COLON CANCERWO09951263A210/14/1999 METHODS AND MODIFIED CELLS FOR THE TREATMENTOF CANCERWO09949034A109/30/1999 BREAST CANCER ANTIGENWO09946392A109/16/1999 METHODS AND COMPOSITIONS OF CHEMOKINE-TUMORANTIGEN FUSION PROTEINS AS CANCER VACCINESJP11237381A208/31/1999 METHOD FOR FITTING HUMAN OR ANIMALTRANSPLANTATION TISSUE TO RECIPIENT AND METHOD FOR DETECTING TUMORANTIGEN IN HUMAN OR ANIMALWO09938954A108/05/1999 A UNIVERSAL IMMUNOMODULATORYCYTOKINE-EXPRESSING BYSTANDER CELL LINE AND RELATED COMPOSITIONS ANDMETHODS OF MANUFACTURE AND USEWO09924566A105/20/1999 TUMOR-SPECIFIC ANTIGENS, METHODS FOR THEIRPRODUCTION AND THEIR

USE FOR IMMUNIZATION AND DIAGNOSISEP00910646A104/28/1999 BRAIN GLYCOGEN PHOSPHORYLASE
CANCER ANTIGENEP00882130A212/09/1998 HUMAN CANCER ANTIGEN OF TYROSINASE-RELATEDPROTEIN 1
AND 2 AND GENES ENCODING SAMEWO09850551A111/12/1998 RAGE1-LIKE
PROTEINWO09846769A110/22/1998 COMPOSITION AND METHOD FOR INDUCING AN IMMUNERESPONSE
AGAINST TUMOUR-RELATED ANTIGENSEP00521842B109/16/1998 Tumor antigen specific
antibodyWO09833511A108/06/1998 STRUCTURALLY MODIFIED PEPTIDES RESISTANT TOPEPTIDASE
DEGRADATIONWO09816246A104/23/1998 CYTOKINE ENHANCED IMMUNOTHERAPY FOR
BRAINTUMORSWO09816238A204/23/1998 CANCER IMMUNOTHERAPY USING TUMOR CELLSCOMBINED WITH
MIXED LYMPHOCYTESWO09800163A101/08/1998 INDUCTION OF CTLs SPECIFIC FOR NATURALANTIGENS BY
CROSS-PRIMING IMMUNIZATIONWO09749817A112/31/1997 BRAIN GLYCOGEN PHOSPHORYLASE CANCER
ANTIGENWO09749421A112/31/1997 GM-CSF ADMINISTRATION FOR THE TREATMENT ANDPREVENTION OF
RECURRENCE OF BRAIN TUMORSEP00721504A107/17/1996 IMMUNOREACTIVE PEPTIDE SEQUENCE FROM A
43 KDHUMAN CANCER ANTIGENJP07318562A212/08/1995 ANTIBODY HAVING SPECIFICITY TO
ANTIGENRELATING TO MAMMARY CANCER AND ANTIGEN MEASURING METHODJP07092160A204/07/1995
COLLECTING DEVICE, TESTING AND COLLECTINGDEVICE, TESTING METHOD, AND MEASURING
METHODWO09506725A103/09/1995 IMMUNOREACTIVE PEPTIDE SEQUENCE FROM A 43 KDHUMAN CANCER
ANTIGENEP00266663B101/18/1995 Chimeric antibody with specificity to humantumor
antigenJP06157347A206/03/1994 SELECTIVE CARCINOSTATIC AGENTJP06157346A206/03/1994 SELECTIVE
CARCINOSTATIC AGENTJP06141884A205/24/1994 AMINO ACID SEQUENCE OF ANTICANCER
HUMANMONOCLONAL ANTIBODY AND DNA BASE SEQUENCE CAPABLE OF CODING
THESAMEEP00521842A301/26/1994 Tumor antigen specific antibodyEP00521842A201/07/1993 Tumor antigen
specific antibodyJP04212063A208/03/1992 ASSAY OF HUMAN LUNG TUMOR ANTIGEN AND
REAGENTTHEREFORJP04159290A206/02/1992 GM3-ANALOGOUS COMPOUND AND METHOD
FORSYNTHESIZING THE SAMEJP04054131A202/21/1992 SYNTHETIC VACCINE FOR SPECIFICALLY
INDUCINGCYTOTOXIC T-LYMPHOCYTEJP04001138A201/06/1992 ANTITUMOR
AGENTJP02306923A212/20/1990 NEW ANTIBODY TRANSPORT SYSTEM FOR BIORESPONSEREGULATORY
SUBSTANCEEP00171083B111/14/1990 Monoclonal antibody, process for preparingsame, reagent for detecting
cancer antigen containing the monoclonalantibody and process for preparing sameJP01309677A212/14/1989
MICROORGANISMJP01291790A211/24/1989 NOVEL MONOCLONAL ANTIBODY AND
HYBRIDOMAJP01238542A209/22/1989 ANTISERUM AND PRODUCTION THEREOFJP01156928A206/20/1989
ANTI-CANCER ANTI-SERUM AND PRODUCTIONTHEREOFJP63290898A211/28/1988 HUMAN IMMUNOGLOBLIN
PRODUCING HUMAN/HUMANHYBRIDOMA SPECIFIC TO CANCER-RELATED ANTIGEN AND ANTIBODY
PRODUCEDTHEREBYEP00288082A210/26/1988 A tumor specific assay for CA125 ovariancancer
antigenJP63251093A210/18/1988 NOVEL MONOCLONAL ANTIBODY AGAINST SMALL CELLLUNG CANCER
ANTIGEN AND MOUSE-HYBRIDOMA PRODUCING THEABOVE-MENTIONED ANTIBODYJP63139134A206/10/1988
T CELL ACTIVATOREP00266663A105/11/1988 Chimeric antibody with specificity to humantumor
antigenWO08803145A105/05/1988 CHIMERIC ANTIBODY WITH SPECIFICITY TO HUMANTUMOR
ANTIGENEP00259773A203/16/1988 A novel antibody specific for a cancerantigenJP62238465A210/19/1987
QUANTIFICATION OF ADENOCARCINOMATOUSANTIGENJP61234357A210/18/1986 ASSAY OF HUMAN LUNG
CANCER ANTIGENJP61044900A203/04/1986 MONOCLONAL ANTIBODY AND REAGENT FOR
DETECTINGCANCER ANTIGENEP00171083A202/12/1986 Monoclonal antibody, process for preparingsame,
reagent for detecting cancer antigen containing the monoclonalantibody and process for preparing
sameJP59142466A208/15/1984 MEASURING METHOD OF MATERIAL PROVIDED WITHANTIGEN- DETERMINING
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US0612076709/19/2000 Chimeric antibody with specificity to human Bcell surface antigen; US0609091407/18/2000 CTLA4/CD28Ig hybrid fusion proteins and usesthereof; EP00721469B101/05/2000 ANTI-GP39 ANTIBODIES AND USES THEREFOR; US0601090201/04/2000 Antibody heteroconjugates and bispecificantibodies for use in regulation of lymphocyte activity; US0599380011/30/1999 Methods for prolonging the expression of aheterologous gene of interest using soluble CTLA4 molecules and anantiCD40 ligand; US0597731811/02/1999 CTLA4 receptor and uses thereof; US0596851010/19/1999 CTLA4 receptor and uses thereof; US0594551308/31/1999 Fusion proteins comprising gp39 and CD8; WO09942077A208/26/1999 COMPOSITIONS AND METHODS FOR REGULATINGLYMPHOCYTE ACTIVATION; US0591656006/29/1999 Methods for inhibiting an immune response byblocking the GP39/CD40 and CTLA4/CD28/B7 pathways and compositionsfor use therewith; EP00757099A305/26/1999 CTLA4 mutant molecules and uses thereof; US0588579603/23/1999 CTLA4 receptor and uses thereof; US0588557903/23/1999 CTLA4 receptor and uses thereof; US0587671803/02/1999 Methods of inducing T cell non-responsivenessto transplanted tissues and of treating graft-versus-host-diseasewith anti-gp39 antibodies; EP00892643A101/27/1999 METHODS FOR INHIBITING AN IMMUNE RESPONSE BYBLOCKING THE GP39/CD40 AND CTLA4/CD28/B7 PATHWAYS AND COMPOSITIONSFOR USE THEREWITH; EP00445228B101/20/1999 IMMUNOTHERAPY INVOLVING CD28 STIMULATION; US0585179512/22/1998 Soluble CTLA4 molecules and uses thereof; US0584409512/01/1998 CTLA4 Ig fusion proteins; US0580773409/15/1998 Monoclonal antibodies and FV specific for CD2antigen; EP00606217B109/02/1998 CTL4A RECEPTOR, FUSION PROTEINS CONTAINING ITAND USES THEREOF; US0579557208/18/1998 Monoclonal antibodies and FV specific for CD2antigen; US0578645607/28/1998 Bp 50-specific antibodies and fragmentsthereof; US0577325306/30/1998 MYPPPY variants of CTL A4 and uses thereof; US0577019706/23/1998 Methods for regulating the immune responseusing B7 binding molecules and IL4-binding molecules; US0574703705/05/1998 Anti-GP39 antibodies; US0574630605/05/1998 Switch having stackable fuses; EP00832227A104/01/1998 METHOD FOR PROLONGING THE EXPRESSION OF AGENE OF INTEREST USING SOLUBLE CTLA4 MOLECULES; US0572110802/24/1998 Chimeric antibody with specificity to human Bcell surface antigen; EP00585943B102/11/1998 Soluble ligands for CD40; US0570985901/20/1998 Mixed specificity fusion proteins; US0567718010/14/1997 Chimeric antibody with specificity to human Bcell surface antigen; WO09734633A109/25/1997 METHODS FOR INHIBITING AN IMMUNE RESPONSE BYBLOCKING THE GP39/CD40 AND CTLA4/CD28/B7 PATHWAYS AND COMPOSITIONSFOR USE THEREWITH; US0563748106/10/1997 Expression vectors encoding bispecific fusionproteins and methods of producing biologically active bispecificfusion proteins in a mammalian cell; WO09720048A206/05/1997 MODIFIED SFV MOLECULES WHICH MEDIATE ADHESIONBETWEEN CELLS AND USES THEREOF; US0560924503/11/1997 Modular switch interior assembly and

method ofassembling same; EP00613944A303/05/1997 Methods for regulating the immune responseusing CTLA4-binding molecules and IL4-binding molecules; EP00757099A202/05/1997 CTLA4 mutant molecules and uses thereof; WO09639514A112/12/1996 METHOD FOR PROLONGING THE EXPRESSION OF AGENE OF INTEREST USING SOLUBLE CTLA4 MOLECULES; US05558075612/03/1996 B7IG fusion protein; US05540926O7/30/1996 Soluble and its use in B cell stimulation; EP00721469A107/17/1996 ANTI-GP39 ANTIBODIES AND USES THEREFOR; US05521288O5/28/1996 CD28IG fusion protein; EP00610046A304/24/1996 Expression vectors encoding bispecific fusionproteins and methods of producing biologically active bispesificfusion proteins in a mammalian cell; US05500362O3/19/1996 Chimeric antibody with specificity to human Bcell surface antigen; EP00336379B102/07/1996 Antibody heteroconjugates for use inregulation of lymphocyte activity; EP00682039A111/15/1995 CTLA4 molecules and IL4-binding molecules anduses thereof; US05434T3107/18/1995 Chimeric CTLA4 receptor and methods for itsuse; JP07069928A203/14/1995 INHIBITION OF TUMOR CELL GROWTH BYADMINISTRATION OF B7-TRANSFECTED CELLS; EP00600591A303/01/1995 JP07069914A203/14/1995 IMMUNE RESPONSE-REGULATING COMPOSITION; EP00595659A301/11/1995 Inhibition of tumor cell growth byadministration of B7-transfected cells; EP00626447A111/30/1994 Extracellular matrix receptor ligands thatmodulate leukocyte function; EP00613944A209/07/1994 Monoclonal ahtibodies and Fv specific for cd2antigen; EP00610046A208/10/1994 Methods for regulating the immune responseusing CTLA4-binding molecules and IL4-binding molecules; US05341273O8/23/1994 Electrical load center; EP00606217A107/20/1994 Expression vectors encoding bispecific fusionproteins and methods of producing biologically active bispesificfusion proteins in a mammalian cell; EP00585943A307/06/1994 CTL4A RECEPTOR, FUSION PROTEINS CONTAINING ITAND USES THEREOF; EP00308936B107/06/1994 Soluble ligands for CD40; EP00600591A206/08/1994 Antibody heteroconjugates for the killing ofHIV-infected cells; EP00555880A305/11/1994 Inhibition of tumor cell growth byadministration of B7-transfected cells; EP00595659A205/04/1994 The CD40CR receptor and ligands therefor; EP00585943A203/09/1994 Extracellular matrix receptor ligands thatmodulate leukocyte function; EP00555880A208/18/1993 Soluble ligands for CD40; US05247069O9/21/1993 Ligands and methods for augmenting B-cellproliferation; EP00507256A306/16/1993 The CD40CR receptor and ligands therefor; EP00537293A104/21/1993 Tyrosine phosphorylation in protozoa; JP05132429A205/28/1993 LIGAND FOR CD28 RECEPTOR ON B CELLS ANDMETHODS; US05182368O1/26/1993 TYROSINE PHOSPHORYLATION IN PROTOZOA; EP00445228A109/11/1991 Ligands and methods for augmenting B-cellproliferation; WO09300431A101/07/1993 CTL4A RECEPTOR, FUSION PROTEINS CONTAINING ITAND USES THEREOF; EP00507256A210/07/1992 IMMUNOTHERAPY INVOLVING CD28 STIMULATION; US05134543O7/28/1992 Tyrosine phosphorylation in protozoa; WO09200092A101/09/1992 LIGAND FOR CD28 RECEPTOR ON B CELLS ANDMETHODS; EP00445228A109/11/1991 Electrical load center; WO09005541A105/31/1990 IMMUNOTHERAPY INVOLVING CD28 STIMULATION; USD031885408/06/1991 Combined housing and bus bar support panel foran electrical load center; WO09101583A102/07/1991 IMPROVED ELECTRICAL LOAD CENTER; WO09005541A105/31/1990 Antibody heteroconjugates for the killing ofHIV-infected cells; EP00308936A302/14/1990 Antibody heteroconjugates for use inregulation of lymphocyte activity; EP00336379A301/31/1990 Chimeric antibody with specificity to human Bcell surface antigen; JP01304356A212/07/1989 ANTIBODY HETEROCONJUGATE FOR REGULATINGLYMPHOCYTE ACTIVITY; EP00336379A210/11/1989 Antibody heteroconjugates for use inregulation of lymphocyte activity; JP01163134A206/27/1989 ANTIBODY HETEROCONJUGATE FOR KILLINGHIV-INFECTED CELL; EP00308936A203/29/1989 Antibody heteroconjugates for the killing ofHIV-infected cells; WO08804936A107/14/1988 CHIMERIC ANTIBODY WITH SPECIFICITY TO HUMAN BCELL SURFACE ANTIGEN; EP00274394A207/13/1988 Chimeric antibody with specificity to human Bcell surface antigen; 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The invention also contemplates multifunctional ligands comprising various combinations and permutations of such ligands including pairs and three different such ligands.including multifunctional ligands including such combinations

and a ligand which binding to a lymphatic vessel associated ligand.Additional pertinent references pertaining to formation of antibody dimmers, microarrays of (and tissue microarrays) proteins including heterofunctional proteins and recombinant, ligands having application to the invention, and phage or ribosome display strategies having relevance herein include Zhu H. et al. 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With respect to technologies having application herein see also Immunity 2001 Apr;14(4):437-46 The immunological barrier to xenotransplantation.Cascalho M, Platt JL.; WO 01/43779; WO 01/42285; WO 98/10795; WO 01/40803; WO 00/14212; Gastroenterology 2001 May;120(6):1330-8 An engineered human antibody to TNF (CDP571) for active Crohn's disease: a randomized double-blind placebo-controlled trial. Sandborn WJ; WO 01/44282; WO 01/40309; WO 01/40274; WO 01/44300; Ann Rheum Dis 2001 May;60(5):433 Cancer and autoimmunity: autoimmune and rheumatic features in patients with malignancies, Abu-Shakra M, et al.; WO 01/40468; WO 01/40307; WO 01/42297; WO 01/42294; WO 01/42296; WO 01/40456; WO 01/40308; WO 01/42306; Curr Opin Immunol 2001 Apr;13(2):134-40 Immunity against cancer: lessons learned from melanoma. Houghton AN, Gold JS, Blachere NE.; WO 01/42288; WO 01/42288; WO 01/43771; WO 01/42308; WO 01/41804; WO 01/39722; WO 01/44808; WO 01/43770; WO 01/16166; WO 01/41803; WO 01/13110; WO 00/32752; WO 98/33528; WO 01/43695; J Am Pharm Assoc (Wash) 2001 May-Jun;41(3):383-91 Magic bullets finally find their mark.; Leukemia 2001 Apr;15(4):675-6; WO 01/44301; Anticancer Res 2001 Jan-Feb;21(1B):621-7 Immunotherapy for recurrent colorectal cancers with human monoclonal antibody SK-1. Koda K et al.; WO 01/10911; WO 01/42506; Int J Clin Pract 2001 Apr;55(3):211-6 Tumour necrosis factor as a therapeutic target in rheumatoid arthritis and other chronic inflammatory diseases: the clinical experience with infliximab; WO 01/44472; WO 01/40302; WO 01/40305)

With respect to surface plasmon resonance measurements of affinity see US6111652:High throughput surface plasmon resonance analysis system US0620842203/27/2001 Surface plasmon sensor EP01080365A103/07/2001 SURFACE PLASMON RESONANCE SENSOR FOR THE SIMULTANEOUS MEASUREMENT OF A PLURALITY OF SAMPLES IN FLUID FORM EP01079225A102/28/2001 Surface plasmon sensor for analyzing liquid sample or humid atmosphere WO00109388A102/08/2001 INSTRUMENTS, METHODS AND REAGENTS FOR SURFACE PLASMON RESONANCE WO00106236A101/25/2001 HIGH THROUGHPUT ANALYSIS OF MOLECULAR INTERACTION USING SURFACE PLASMON RESONANCE EP01068511A101/17/2001 ARRANGEMENT FOR SURFACE PLASMON RESONANCE SPECTROSCOPYWO00070328A111/23/2000 SURFACE PLASMON RESONANCE DETECTION WITH HIGHANULAR RESOLUTION AND FAST RESPONSE TIME EP 1054290A2 1/22/2000 Light modulator controlled by surface plasmon waves US0612209109/19/2000 Transmissive surface plasmon light valve US0611165208/29/2000 High throughput surface plasmon resonance analysis system as well as Dimensions of antigen recognition and levels of immunological specificity. Adv Cancer Res. 2001;80:147-87. Use of optical biosensors for the study of mechanistically concerted surface adsorption processes.Anal Biochem. 2001 Jan 15;288(2):109-25 Experimental design for analysis of complex kinetics using surface plasmon resonance. Methods. 2000 Mar;20(3):310-8. , and references cited in the foregoing references.

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With respect to making multifunctional ligands see also USP 5,731,168 and 5,821,333.

With respect to TNF and TNFR variants, and functional fragments thereof, for use as antibody targets and binding moieties with respect to various aspects of the invention herein see WO 00/67793, WO 01/30300, WO 01/49321, WO 00/62790, WO 01/03720, WO 00/60079, WO 97/46686, WO 01/41803, WO 01/38526, WO 01/37874, WO 01/12812, WO 01/12671, WO 01/05834, WO 01/03720, WO 00/77191 WO 00/73321, WO 00/71150, WO 00/67793, WO 00/67034, WO 00/66608, WO 00/66156., WO 01/24811, as well as references cited therein. Many other TNFR variants and TNF analogs are known in the art.

With respect to cytokines and cytokine receptors see also the latest editions of Cytokine Reference: A Compendium of Cytokines and Other Mediators of Host Defense by Joost J. Oppenheim (Editor), Jan Vilcek, Nicos A. Nicola (Editor); Cytokine Molecular Biology : A Practical Approach by Frances R. Balkwill (Editor), Fran Balkwill (Editor); Guidebook to Cytokines and Their Receptors by Nicos Nicola (Editor); The Cytokine Network and Immune Functions by Jacques Theze; Novel Cytokine Inhibitors by Gerry A. Higgs (Editor), Brian Henderson (Editor); Homology Folding of Proteins : Application to Cytokine Engineering by Subhashini Srinivasan; Cytokines and Cytokine Receptors (2001); International Review of Experimental Pathology : Cytokine-Induced Pathology, Part B : Inflammatory Cytokines, Receptors, and Disease by G.W. Richter, Kim Solez (Editor).

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With respect to ligands involved in mediating apoptosis see also WO0144808 METHODS OF DIAGNOSIS AND TREATMENT BY BINDING P75/AIRM1 WO0144282 BCL-G POLYPEPTIDES, ENCODING NUCLEIC ACIDS AND METHODS OF USE US6242569 Regulators of apoptosis EP1106183 Antibodies to erbB2 and their therapeutic uses WO0136594 Mcl-1 GENE REGULATORY ELEMENTS AND A PRO-APOPTOTIC Mcl-1 VARIANT US2001001712 Monoclonal antibodies having property of causing apoptosis WO0134798 CLONING AND CHARACTERIZATION OF VIRAL IAP ASSOCIATED FACTOR (VIAF) IN SEVERAL ORGANISMS CZ20000907 Monoclonal antibody inducing apoptosis HU0003513 MONOCLONAL ANTIBODY INDUCING APOPTOSIS EP1094316 Method for the detection of DNA replicating cells US6207452 Antibody of the anti-proliferation domain of human Bcl-2 WO0123568 NOVEL MEMBERS OF THE IAP GENE FAMILY US6190661 Methods and compositions for the use of apurinic/apyrimidinic endonucleases EP1087993 FAS PEPTIDES AND ANTIBODIES FOR MODULATING APOPTOSIS WO0119861 APO-2 RECEPTOR ANTIBODIES US6184034 Deoxyribonuclease II proteins and cDNAS US6172211 Nucleic acid encoding tag7 polypeptide WO0118042 APOPTOSIS PROTEINS WO0116180 CD40 LIGAND AND CD40 AGONIST COMPOSITIONS AND METHODS OF USE WO0116170 NOVEL CARD PROTEINS INVOLVED IN CELL DEATH REGULATION WO0144808 METHODS OF DIAGNOSIS AND TREATMENT BY BINDING P75/AIRM1 WO0144282 BCL-G POLYPEPTIDES, ENCODING NUCLEIC ACIDS AND METHODS OF USE US6242569 Regulators of apoptosis EP1106183 Antibodies to erbB2 and their therapeutic uses WO0136594 Mcl-1 GENE REGULATORY ELEMENTS AND A PRO-APOPTOTIC Mcl-1 VARIANT US2001001712 Monoclonal antibodies having property of causing apoptosis WO0134798 CLONING AND CHARACTERIZATION OF VIRAL IAP ASSOCIATED FACTOR (VIAF) IN SEVERAL ORGANISMS CZ20000907 Monoclonal antibody inducing apoptosis HU0003513 MONOCLONAL ANTIBODY INDUCING APOPTOSIS EP1094316 Method for the detection of DNA replicating cells US6207452 Antibody of the anti-proliferation domain of human Bcl-2 WO0123568 NOVEL MEMBERS OF THE IAP 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As stated above, in a related but also independent aspect, the invention contemplates a method of screening for an antibody which preferentially binds to a ligand when bound to a first receptor relative to another second receptor by screening for antibodies (eg. by phage display, ribosome display, etc.) which bind to the ligand eg. a cytokine,

when bound in situ to the first receptor, and selecting among them those that bind to the ligand eg. cytokine but do not bind (substractive screening) or bind with lesser affinity when bound to the cytokine to the second receptor, as well as to antibodies and multifunctional ligands created by this method (see also USP 6,046,048 and WO 99/12973 and references cited therein with respect to TNF family of receptors). Variations in the extracellular domains of such receptors are known and can be ascertained by methods known to those skilled in the art. Accordingly the invention is directed to an antibody characterized in that it binds to an epitope on the ligand which permits the ligand to bind, while the antibody is bound to it, to a first receptor but not a second receptor: In a preferred embodiment both are cell surface receptors. In a preferred embodiment the ligand is a natural ligand, preferably a growth factor, cytokine or chemokine. In another embodiment one of the receptors is a soluble receptor. The invention is also directed to a method of evaluating the pleitropic effects of a natural ligand by administering the said antibody including antigen binding fragments thereof and MRUs) and monitoring its effects. The invention contemplates that this antibody is a first or second moiety of a multifunctional ligand disclosed herein: Examples of receptors include the classes of VEGF receptors (see also 1:Sheppard D.Integrin-mediated activation of transforming growth factor-beta(1) in pulmonary fibrosis.Chest. 2001 Jul;120(1 Suppl):S49-53. Chow D, Ho J, Nguyen Pham TL, Rose-John S, Garcia KC.In vitro reconstitution of recognition and activation complexes between interleukin-6 and gp130.Biochemistry. 2001 Jun 26;40(25):7593-603. 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Review.26: Staunton D, Hudson KR, Heath JK.The interactions of the cytokine-binding homology region and immunoglobulin-like domains of gp130 with oncostatin M: implications for receptor complex formation:Protein Eng. 1998 Nov;11(11):1093-102).

With respect to markers that are useful for differentiating between various populations and sub-populations of cells, see also Human IL-18 Receptor and ST2L Are Stable and Selective Markers for the Respective Type 1 and Type 2 Circulating Lymphocytes, Woon Ling Chan, Nada Pejnovic, Christine A. Lee, and Nadia A. Al-Ali, J Immunol 2001;167 1238-1244; CD4+CD25 high Regulatory Cells in Human Peripheral Blood, Clare Baecher-Allan, Julia A. Brown, Gordon J. Freeman, and David A. Hafler, J Immunol 2001;167 1245-1253.

In another aspect the invention is directed to multifunctional ligand comprising at least a first moiety which specifically binds to a ligand on the surface of a virus particle that is capable of infecting a mammalian and particularly a human cell including a cancer cell (excluding viruses which are known for use in gene therapy) and is preferably selected from the group consisting viruses which infect substantial populations of individuals including for example influenza virus and at least a second moiety which specifically recognizes a cancer cell, in one embodiment preferably a marker present on multiple different cancer types, especially cancer types that are individually or collectively most prevalent in the general population. In one embodiment such multifunctional ligand is a bispecific, trispecific or tetraspecific antibody. The invention contemplates that such a multifunctional ligand may be used to target such viruses to tumors in a manner which preferentially kills the cancer cells either through the action of the virus and/or by causing the immune response to the virus or virus infected cell to preferentially (relative to non-cancer cells) target the cancer cell for ablation. The invention is also directed to a method of treating cancer by retargeting virus with which an individual is otherwise infected to the cancer cell eg. influenza. The invention also contemplates that the multifunctional ligand includes one or more effector moieties which assist ing killing the virus and/or cancer cell or directing immune cells to the virus and/or cancer cell, if and when present in the individual, for example a moiety which specifically binds to such immune cell eg. a T cell, as discussed above. Accordingly, the invention also contemplates that such multifunctional ligand may be used to treat influenza virus infections and secondarily to act prophylactically as a sentinel against any cancer cells which might develop during the course of the viral infection or a period of immune suppression or increased succeptibility to infection or cancer, including for example, as experienced by individuals with a particular immune suppressive disorder or condition or under treatment with immune suppressive drugs, individuals at risk for cancer or recurrence of a cancer, individuals of a particular age group, individuals experiencing a period of unusual stress which increases their succeptibility to disease or infection. The invention also contemplates that such a moiety is used in concert with prior immunization against the virus, so that the augemented immune response to the virus benefits the treatment of the cancer cells (see for example USP 6169175 and the art cited therein). The invention also directed to such a virus (excluding viruses known for use in gene therapy applications eg. adenovirus) which is engineered to expresses on its surface a cancer targeting moiety such as a scFv (see for example EP 1038967, WO 94/10323 and the art cited therein). The invention is also directed to a method of identifying the expression or over-expression of cell surface markers associated with infection by such a virus, by substractive screening relative to markers also expressed on non-infected such cells, for example using phage display or the like. Such markers may be used for vaccine-type or other immunotherapeutic strategies. Anti-virus markers including influenza virus markers and methods of identifying new such markers are well known in the art (see for example USP 5589174) (see also The role of the antibody response in influenza virus infection., Gerhard W.,Curr Top Microbiol Immunol 2001;260:171-90, Fernandez-Sesma A, Schulman JL, Moran TM.A bispecific antibody recognizing influenza A virus M2 protein redirects effector cells to inhibit virus replication in vitro.J Virol. 1996 Jul;70(7):4800-4; Todorovska A, Roovers RC, Dolezal O, Kortt AA, Hoogenboom HR, Hudson PJ. Design and application of diabodies, triabodies and tetrabodies for cancer targeting. J Immunol Methods. 2001 Feb 1;248(1-2):47-66., Staerz UD, Yewdell JW, Bevan MJ. Hybrid antibody-mediated lysis of virus-infected cells. Eur J Immunol. 1987 Apr;17(4):571-4; Fernandez-Sesma A, Schulman JL, Moran TM.A bispecific antibody recognizing influenza A virus M2 protein redirects effector cells to inhibit virus replication in vitro. J Virol. 1996 Jul;70(7):4800-4.)

The invention is also directed to a multifunctional ligand having at least a tumor cell targeting moiety and a moiety which binds to a tumor antigen which is shed from a cancer cell. In a preferred embodiment, the tumor antigen binding moiety preferably does not recognize the portion of the antigen which is most immunogenic and leaves that portion exposed for recognition by the immune system. The invention contemplates generating such preferred antibody or fragment thereof by using an an immune complex between an antibody that binds to such immunogenic portion and the antigen as a target for phage display or generation or polyclonal sera. The invention also contemplates identifying antibodies which recognize immunogenic portions of the antigen by screening patient sera for antibodies which recognize the antigen. The invention also contemplates that such multifunctional ligand includes one or more effector moieties which assist in killing the cancer cell or directing immune cells to the cancer cell, for example a moiety which specifically binds to such immune cell eg. a T cell receptor, as discussed above.

All publications and references therein cited are herein incorporated by reference to the same extent as if each of the individual publications were specifically and individually indicated to be incorporated by reference in its entirety.

Claims

1. A multispecific ligand* with at least two different binding specificities for different target ligands* on the same target cell* and adapted to bind simultaneously to the different target ligands, said multispecific ligand comprising a first target binding moiety which preferentially* recognizes a first target ligand and a second target binding moiety which preferentially recognizes a second target ligand, the first target binding moiety adapted to bind to the first target ligand independently of the second target binding moiety binding to the second target ligand, the first target moiety having an off-rate which at least exceeds the on-rate of the second target binding moiety for the second target ligand to provide opportunity for the second target moiety to bind the second target ligand when the first ligand is bound to the first target ligand, the second target binding moiety having a relatively diminished ability to bind and/or stay bound to the second target ligand independently of the binding of the first target binding moiety to the first target ligand.

2. A multispecific ligand according to claim 1, wherein said first target binding moiety recognizes a target cell-associated* target ligand, for example a ligand which is exclusively expressed, primarily expressed or over-expressed to advantage on the target cell population and said second target binding moiety recognizes a non-target cell-associated target ligand which is present on target cells and non-target cells, for example a receptor, including a decoy receptor.

3. A multispecific ligand according to any of the preceding claims, wherein the intrinsic* affinity of the first target binding moiety is greater than the intrinsic affinity of the second target binding moiety.

4. A multispecific ligand according to any of the preceding claims, wherein the relative affinity of the first target binding moiety is greater than the relative affinity of the second target binding moiety.

5. A multispecific ligand according to any of the preceding claims, wherein the relative on-rate* of the first target binding moiety is greater than the relative on-rate of the second target binding moiety.

6. A multispecific ligand according to any of the preceding claims, wherein the intrinsic on-rate* of the first target binding moiety is greater than the intrinsic on-rate of the second target binding moiety.

7. A multispecific ligand according to any of the preceding claims, wherein the off-rate contribution to the affinity of the first target binding moiety is proportionally greater than the off-rate contribution to the affinity of the second target binding moiety.

8. A multispecific ligand according to any of the preceding claims, which is a multispecific antibody.

9. A multispecific ligand according to any of the preceding claims, having a center of mass which favors the binding of first target binding moiety to the first target ligand.

10. A multispecific ligand according to any of the preceding claims, wherein the center of mass is in the Fab portion of the molecule and wherein at least one portion of said multispecific ligand is adapted to advance the leading edge of Fab[1] of the first ligand binding moiety in the direction of flow of a liquid relative to the leading edge of the Fab of the second binding moiety, while being carried by the liquid.

11. A multispecific ligand according to claim any of the preceding claims, wherein the center of mass is located substantially at the center* of the Fab portion of the molecule and wherein the Fab[2] portion of the first ligand binding moiety is longer than the Fab portion of the second binding moiety.

12. A multispecific ligand according to any of the preceding claims, comprising a Fc portion and a hinge portion and wherein one or both of a) the length, amino acid composition or* molecular weight (or various combinations of these interrelated factors) of the Fc portion; and b) the amino acid composition[3] of hinge portion* are selected to increase the circumstantial[4] off-rate of the second ligand binding moiety where the first ligand binding moiety is unbound relative to the circumstantial off-rate of the second ligand binding moiety where the first ligand binding moiety is bound.

13. A multispecific ligand according to any of the preceding claims, wherein the intrinsic[5] affinity of the second ligand binding moiety is greater when the first ligand binding moiety is bound to the first target ligand relative to when it is unbound.

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[1] Fab has to be broadly enough defined to cover a single domain
[2] Fab has to be broadly enough defined to cover a single domain
[3] includes length
[4] shear rate, presence of degrading enzymes
[5] this has to be carefully defined

14. A multispecific ligand* with at least two different binding specificities for different target ligands* on the same target cell* and adapted to bind simultaneously to the different target ligands, said multispecific ligand comprising a first target binding moiety which preferentially* recognizes a first target ligand and a second target binding moiety which preferentially recognizes a second target ligand, and wherein said first target binding moiety recognizes a target cell-associated* target ligand and said second target binding moiety recognizes a non-target cell-associated target ligand which is present on target cells and non-target*[6] cells; and wherein the affinity of the second target binding moiety for the second target is less than that of the first target binding moiety for the first target ligand, the first target binding moiety having an affinity which is at least sufficient for the first target moiety to bind to the first target ligand independently of the second target binding moiety binding to the second target ligand and an off-rate which at least sufficiently exceeds the on-rate of the second target binding moiety for the second target ligand to provide at least sufficient opportunity for the second target moiety to bind the second target ligand when the first target binding moiety is bound to first target ligand, the second target binding moiety having a relatively diminished ability to bind or stay bound to the second target ligand independently of the binding of the first target binding moiety to the first target ligand, such that the multispecific ligand will bind to the target population of cells in preference[7] to the non-target population of cells.

15. A multispecific ligand according to any of the preceding claims, wherein said second target binding moiety comprises a bioresponse modifier bound to a VH or VL or both.
16. A multispecific ligand* with at least two different binding specificities for different target ligands* on the same target cell* and adapted to bind simultaneously to the different target ligands, said multispecific ligand comprising a first target binding moiety which preferentially* recognizes a first target ligand and a second target binding moiety which preferentially recognizes a second target ligand, and wherein the independent affinity of the first and second target

[6] Adverse target
[7] This term needs to be defined in terms of baseline of expected augmented binding even where the affinities would be comparable.

binding moieties to bind to stay bound their respective target ligands is selected to favor binding of the multispecific ligand to a target cell relative to a cell having only one of the target ligands on its surface, and wherein at least the first target binding moiety has an off-rate which at least exceeds the on-rate of the second target binding moiety for the first target binding moiety to provide opportunity for the second target moiety to bind the second target ligand when the first target binding moiety is bound to first target ligand.

17. A multispecific ligand according to any of claims 1 to 13, wherein the affinity of the first target binding moiety is at least 5 times greater than that of the second target binding moiety.
18. A multispecific ligand according to any of claims 1 to 13, wherein the affinity of the first target binding moiety is at least one order of magnitude greater than that of the second target binding moiety
19. A multispecific ligand according to any of claims 1 to 13, wherein the affinity of the first target binding moiety is at least 1.5 orders of magnitude greater than that of the second target binding moiety
20. A multispecific ligand according to any of claims 1 to 13, wherein the affinity of the first target binding moiety is at least two orders of magnitude greater than that of the second target binding moiety
21. A multispecific ligand according to any of claims 1 to 13, wherein the affinity of the first target binding moiety is at least 2.5 orders of magnitude greater than that of the second target binding moiety
22. A multispecific ligand according to any of claims 1 to 13, wherein the affinity of the first target binding moiety is at least three orders of magnitude greater than that of the second target binding moiety
23. A multispecific ligand according to any of claims 1 to 13, wherein the affinity of the first target binding moiety is at least 3.5 orders of magnitude greater than that of the second target binding moiety
24. A multispecific ligand according to any of claims 1 to 13, wherein the affinity of the first target binding moiety is at least four orders of magnitude greater than that of the second target binding moiety
25. A multispecific ligand according to any of claims 1 to 13, wherein the affinity of the first target binding moiety is at least 4.5 orders of magnitude greater than that of the second target binding moiety
26. A multispecific ligand according to any of claims 1 to 13, wherein the affinity of the first target binding moiety is at least five orders of magnitude greater than that of the second target binding moiety
27. A multispecific ligand according to any of claims 1 to 13 or 17 to 26, wherein the intrinsic off-rate of the first target binding moiety is at least five times greater than that of the second target binding moiety
28. A multispecific ligand according to any of claims 1 to 13 or 17 to 26, wherein the intrinsic off-rate of the first target binding moiety is at least one order of magnitude greater than that of the second target binding moiety
29. A multispecific ligand according to any of claims 1 to 13 or 17 to 26, wherein the intrinsic off-rate of the first target binding moiety is at least 1.5 orders of magnitude greater than that of the second target binding moiety

30. A multispecific ligand according to any of claims 1 to 13 or 17 to 26,, wherein the intrinsic off-rate of the first target binding moiety is at least two orders of magnitude greater than that of the second target binding moiety
31. A multispecific ligand according to any of claims 1 to 13 or 17 to 26, wherein the intrinsic off-rate of the first target binding moiety is at least 2.5 orders of magnitude greater than that of the second target binding moiety
32. A multispecific ligand according to any of claims 1 to 13 or 17 to 26, wherein the intrinsic off-rate of the first target binding moiety is at least 3 orders of magnitude greater than that of the second target binding moiety
33. A multispecific ligand according to any of claims 1 to 13 or 17 to 26, wherein the intrinsic off-rate of the first target binding moiety is at least 3.5 orders of magnitude greater than that of the second target binding moiety
34. A multispecific ligand according to any of claims 1 to 13 or 17 to 26, wherein the intrinsic off-rate of the first target binding moiety is at least 4 orders of magnitude greater than that of the second target binding moiety
35. A multispecific ligand according to any of claims 1 to 13 or 17 to 26, wherein the intrinsic on-rate of the first target binding moiety is at least 5 times greater than that of the second target binding moiety
36. A multispecific ligand according to any of claims 1 to 13 or 17 to 26, wherein the intrinsic on-rate of the first target binding moiety is at least one order of magnitude greater than that of the second target binding moiety
37. A multispecific ligand according to any of claims 1 to 13 or 17 to 26, wherein the intrinsic on-rate of the first target binding moiety is at least 1.5 ordersof magnitude greater than that of the second target binding moiety
38. A multispecific ligand according to any of claims 1 to 13 or 17 to 26, wherein the intrinsic on-rate of the first target binding moiety is at least 2 orders of magnitude greater than that of the second target binding moiety